Dissertation on

ROLE OF C-REACTIVE PROTEIN AS A SEVERITY MARKER IN ACUTE PANCREATITIS

Submitted in partial fulfillment of
the requirement for the award of the degree of

M.S. BRANCH – I
(GENERAL SURGERY)

DEPARTMENT OF GENERAL SURGERY
GOVT. STANLEY MEDICAL COLLEGE & HOSPITALS

THE TAMILNADU Dr.M.G.R.MEDICAL UNIVERSITY,
CHENNAI – TAMILNADU.

APRIL – 2013

CERTIFICATE

This is to certify that this dissertation on **"ROLE OF C-REACTIVE PROTEIN AS A SEVERITY MARKER IN ACUTE PANCREATITIS"** presented herein by **Dr.S.VIGNESH**, is the original work done in the Department of General Surgery, Government Stanley Medical College and Hospitals, Chennai in partial fulfillment of requirements of M.S. Branch-I (General Surgery) examination of The Tamilnadu DR.M.G.R. Medical University to be held in September 2006 under guidance and supervision during the academic period of 2010-2013.

PROF.C.BALAMURUGAN,
Assoc. Professor
Department of general surgery,
Govt. Stanley Medical college
Chennai - 600001

M.S., PROF.P.DARWIN,
Professor and H.O.D.
Department of General Surgery,
Govt. Stanley Medical College
Chennai - 600001

Dr.GEETHALAKSHMI,
Dean
Govt. Stanley Medical College& Hospitals
Chennai – 600001

Place : Chennai
Date :

DECLARATION

I, **DR.S.VIGNESH**, solemnly declare that this dissertation, titled **"ROLE OF C-REACTIVE PROTEIN AS A SEVERITY MARKER IN ACUTE PANCREATITIS"** is a bonafide record of work done by me in the Department of General Surgery, Government Stanley Medical College and Hospitals, Chennai under the guidance of my unit chief **PROF.DR. C.BALAMURUGAN, M.S., Assoc.** Prof. of surgery, This dissertation is submitted to The Tamilnadu DR.M.G.R. Medical University, Chennai in partial fulfillment of regulations for the award of M.S. (General Surgery) examination to be held in April 2013.

(*Dr.S.VIGNESH*)

Place : Chennai

Date :

ACKNOWLEDGEMENT

I thank **Dr.GEETHALAKSHMI, M.D.,** Dean , for permitting me to conduct this study in Government Stanley Medical College and Hospitals, Chennai-1.

I , owe my sincere thanks to **Prof**. **DR.P.DARWIN, M.S.,** Prof. & head of surgery department, Government Stanley Medical College and Hospitals, for his valuable guidance , constant encouragement and suggestion during my study.

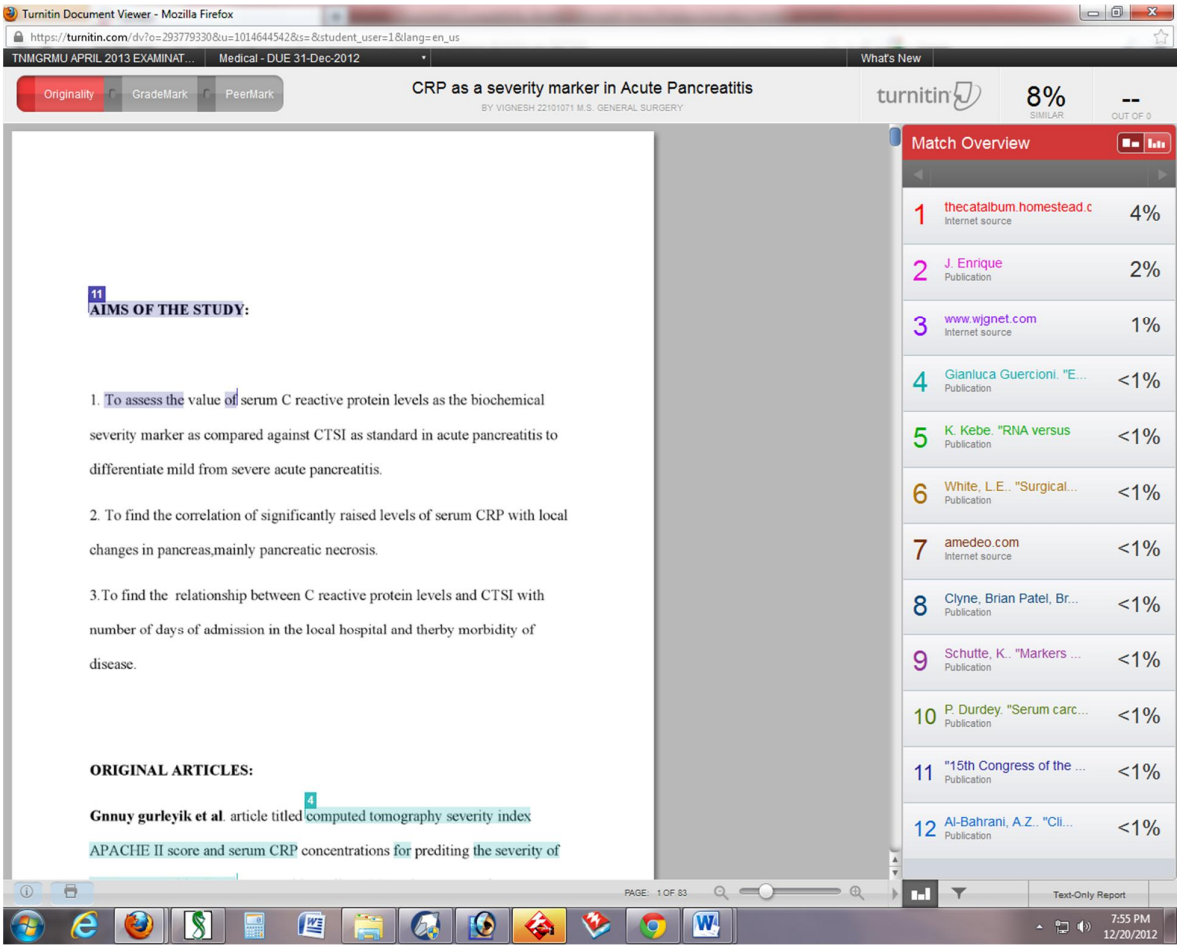
I have great pleasure in expressing my gratitude and humbleness towards my teacher and guide **Prof. DR.C.BALAMURUGAN, M.S.,** under whom I Had the great privilege of working as a post graduate student receiving his constant advice and valuable guidance.

I am also grateful to my teacher Prof**.Dr.J.DEEPAK KABIR,M.S.,DNB.,** under whom also I worked as post graduateand who inspired me in the field of Surgery.He encouraged in preparing the dissertation and inculcated the principles of surgery in me.

I am extremely thankful to the Assistant professors of my unit **Dr.R.VASUKI.M.S, Dr. D.S.KUMARESAN, M.S., Dr.G. VENKATESH,M.S., Dr. JIMJEBAKUMAR,M.S.,** for their valuable suggestion and help. I also thank my Colleagues, CRRIs , and hospital workers for helping me.

Last , but not the least , I thank all my patients with gratitude for their co-operation in this study.

CONTENTS


Turnitin Document Viewer - Mozilla Firefox
https://turnitin.com/dv?o=293779330&u=1014644542&s=&student_user=1&lang=en_us
TNMGRMU APRIL 2013 EXAMINAT...
Medical - DUE 31-Dec-2012
What's New
Originality
GradeMark
PeerMark
CRP as a severity marker in Acute Pancreatitis
BY VIGNESH 22101071 M.S. GENERAL SURGERY
turnitin
8%
SIMILAR
--
OUT OF 0
11
AIMS OF THE STUDY:
1. To assess the value of serum C reactive protein levels as the biochemical severity marker as compared against CTSI as standard in acute pancreatitis to differentiate mild from severe acute pancreatitis.
2. To find the correlation of significantly raised levels of serum CRP with local changes in pancreas,mainly pancreatic necrosis.
3.To find the relationship between C reactive protein levels and CTSI with number of days of admission in the local hospital and therby morbidity of disease.
ORIGINAL ARTICLES:
Gnnuy gurleyik et al. article titled 4 computed tomography severity index APACHE II score and serum CRP concentrations for prediting the severity of
PAGE: 1 OF 83
Match Overview
1 thecatalbum.homestead.c Internet source 4%
2 J. Enrique Publication 2%
3 www.wjgnet.com Internet source 1%
4 Gianluca Guercioni. "E... Publication <1%
5 K. Kebe. "RNA versus Publication <1%
6 White, L.E.. "Surgical... Publication <1%
7 amedeo.com Internet source <1%
8 Clyne, Brian Patel, Br... Publication <1%
9 Schutte, K.. "Markers ... Publication <1%
10 P. Durdey. "Serum carc... Publication <1%
11 "15th Congress of the ... Publication <1%
12 Al-Bahrani, A.Z.. "Cli... Publication <1%
Text-Only Report
7:55 PM
12/20/2012

AIMS OF THE STUDY

1. To assess the value of serum C reactive protein levels as the biochemical severity marker as compared against Computed Tomography Severity Index(CTSI) as standard in acute pancreatitis to differentiate mild from severe acute pancreatitis.

2. To find the correlation of significantly raised levels of serum CRP with local changes in pancreas, mainly pancreatic necrosis.

3. To find the relationship between C reactive protein levels and CTSI with number of days of admission in the local hospital and thereby morbidity of disease.

ORIGINAL ARTICLES:

Gnnuy gurleyik et al. article titled computed tomography severity index APACHE II score and serum CRP concentrations for predicting the severity of acute pancreatitis. Jop. J pancreatitis (online 2005) , department of surgery, department of surgery and department of radiology hay darpara numme education and research hospital, Istanbul turkey concluded that CTSI is a better marker and correlates with the clinical course , severity o f disease and has better accuracy rates when compared with APACHE II and CRP level. And levels of CRP and

APACHE II does not give the extent of local inflammation. And complication which is given by CTSI.

2. **AD et al Meyer**, article titled C reactive protein an aid to assessment and monitoring of acute pancreatitis j clinical pathol 1984, university, Department of surgery General infirmary Leeds and the unit for cancer research , university of Leeds, compared CRP with alpha 1 anti chymotrypsin and alpha 1 protease inhibitor using WBC count and ESR as reference data, conclude that CRP differentiates mild and severe attacks with greatest precision.and serial elevated values of CRP at the end of 1 week of admission can differentiate patients who develop local complication and collection.

3. **Raffaele Pezzilli et al**, article titled assessment of severity of acute pancreatitis a comparison between old and recent modalities used to evaluate perennial problem. World journal of gastroenterology1999, august compared clinical biochemical and radiological criteria. For assessing severity and concluded that at present CRP is the marker which is earliest to perform and which has lowest cost among all markers.

4. **Chun Chia Chen et all.** Article titled serum markers in the early assessment of acute pancreatitis which is most useful. Jichin med assoc

2004:67:439-441 Division of gastroenterology, Department of medicine. Taipei veterans general hospital and national Yang ming university school of medicine, Taiwan. Concluded that serum interleukin 6 levels on the first day and CRP on the second day are useful for early prediction of severity of acute pancreatitis.

5. **Ahmed z et al**, article titled clinical laboratory assessment of acute pancreatitis. Clinica chimica acta (2005) 26-48, department of surgery Manchester royal infirmary. Manchester concluded that CRP is both a marker of severity and pancreatic necrosis in acute pancreatitis.

6. **M.T. Hamalainen et al**., article titled do normal leukocyte and CRP on admission exclude a life threatening attack of acute pancreatitis. Scandinavian journal of surgery 91-352-356, Department of surgery university of Turkey, Finland concluded that it is very unlikely that AP episode is life threatening with normal WBC and CRP values at admission.

REVIEW OF LITERATURE

History

Ambrose pare, a French surgeon is the first to describe pancreatitis. In the 17th and early 18th century Johann Wirsung and Santorini described Main Pancreatic Duct and Accessory Pancreatic Duct respectively.

In 1862, **la Dentu** was the first surgeon to operate on pancreatitis.In 19th century clinical description of pancreatitis was given by Huber Fitz who differentiated suppurative, haemorrhagic and gangrenous form of disease.

In 1925, **George Andrew Moynihan** explained pancreatitis as a important inflammatory disorder of pancreas. Closely followed by **Elman.R** in 1929, giving the associate of serum amylase with pancreatitis.

First prognostic index , the Ransons scoring system was given by **John HL Ranson** in 1974 which goes by his name. The basis for our understanding of pancreatitis and its management both surgical and conservative was given by him.

1978-glascow scoring system **Clement .W.Imrie**

1981-APACHE **William A Knaws**

Inaccurate and so lead to better system

APACHE II

1989- **Balthazar** after the invent of CT, its usefulness in diagnosis and assessing severity of pancreatitis.

1992- **Atlanta classification system**- definition for different terminologies

Surgical anatomy:

It is the retroperitoneal organ situated behind lesser omentum and stomach. Its extension is from c-loop of duodenum to splenic hilum.The gland is yellow tan coloured and it is multi lobulated.

Posterior relation- IVC, right renal vein, SMC vessels, aorta at L1 and splenic vein.

Divided into head, neck, body and tail.Head is situated in c loop of duodenum.Neck lies over SMC vessels and portal vein. Part of head

passing behind the SM vein to the left is Uncinate process. Tail extends upto hilum of spleen.

Blood supply:

Arterial:

Head and neck-arcades from hepatic and gastroduodenal of celiac and branch from first part of SMA.

Body and tail- arcade from splenic artery.

Vein- along SMC, splenic and portal vein.

Lymphnode areas:

Head: portal, sub pyloric, mesenteric, mesocolic and aorto caval nodes. Body and tail: aortocaval, celiac, mesenteric, mesocolic and splenic hilum nodes.

Nerve supply:

Both sympathetic and parasympathetic innervation . Sympathetic nerves carry pain sensation and are targets during sphlancnectomy done for pain relief in chronic pancreatitis.

Pre ganglionic fibres arise from sympathetic ganglia in thorax relays at celiac ganglia from where post ganglionic fibres arise and supply the gland.

Microanatomy:

It is organised into units termed acini and islets of Langerhans which are exocrine and endocrine respectively.

Acinar cells- Polarised synthetic secretory cells with golgi and zymogen granules at its apex-secretes about 1 litre of pancreatic fluid per day rich in enzymes and bicarbonate.

Islets of Langerhans has rich blood supply 20% of total blood supply eventhough they are 1-2 % of pancreatic mass. Centrally in the islets cells are the B cells – secrete insulin (60-80% of cells) peripherally are the cells which secrete glucagon(15-20%) Somatostatin and Pancreatic polypeptide(15-20%).

Physiology of pancreas:

Both endocrine and exocrine functions.

In the exocrine part the acinar cells secrete enzymes and intercalated duct cells secrete electrolytes.Its secretion is regulated by secretin CCK and by reflux mechanism.

All enzymes are secreted as inactive proenzymes these (Trypsinogen) are activated by intestinal enterokinase (Enteropeptidase) into active Trypsin. Inturn Trypsin is the activator of other enzymes secreted by pancreas namely Chymotrypsinogen, Phospholipase A2 and other pro enzymes and this reaction is autocatalytic once initiated. Normally pancreas contains Trypsin inhibitors.

Phospholipase A2 removes a fatty acid from lecithin to form hydro lecithin which damages cell membrane. This enzyme is the reason for the destruction of pancreatic tissue and fat necrosis. In acute pancreatitis only a small amount of pancreatic enzymes leaks into the circulation but in active inflammation of the gland this level increases markedly and they acts as markers and have in diagnosing acute pancreatitis.

Acute pancreatitis:

Etiology:

Majority of cases of acute pancreatitis are due to alcohol and gall stones (80-90%). In United States of America , alcohol is deemed as

cause of majority of cases, where in Asia and United Kingdom the most common cause is gall stones. In India even though gall stone is considered as the most common cause, ethanol induced pancreatitis is on rise particularly in south India. Idiopathic acute pancreatitis constitute upto 30% of cases. Other causes are infection, systemic disease, trauma, hereditary and others.

Causes:

Obstructive causes:

Biliary calculi (gall bladder and CBD calculi)

Tumours of pancreas and ampulla

Foreign bodies at the ampulla

Other rare causes:

Diverticulum in duodenum

Choledochocele

Pancreatic divisum with constricted and small accessory duct

Drug induced:

Alcohol-Ethanol, Methanol

Sodium Valproate, Estrogen

Anti cancer drugs- Azathioprine, Mercapto purine

Antibiotics- Metronidazole Pentamidine Tetra cycline

Sulphonamides

others-Cimetidine, Furosemide, Acetaminophen

Idiopathic

Hereditary

ERCP induced

Hypercalcemia

Hyperlipidemia

Infection –both bacterial and viral

Vasculitis-PAN, SLE

Others:Cystic fibrosis

Crohn's disease

Pathogenesis:

Mechanism: Obstructive

Toxic

Genetic

Obstructive:

Mechanism of pancreatic injury by bile stone passage is unclear

Theories:

In 1901, **Opies theory**, bile retrograde reflux from CBD into MPD through a common channel.It has been proved wrong due to the absence of long common channel, pressure in MPD exceeds that in CBD and so only pancreatic juice only can enter bile duct.

Duodenal reflux theory:

Stone passing through the sphincter of oddi dilated and loosens the sphincter thereby allowing reflux into the CBD, which is also disproved by the absence of pancreatitis with all patients undergoing sphincterotomy and sphincter incompetence.

Ductal hypertension theory:

Bile stone obstructing the MPD secretion collect in the duct and disrupt and enzymes leak out into the parenchyma, but only zymogen and inactive form of enzymes. It is possible that ductal hypertension has other effects that cause intraductal and parenchymal activation of enzymes.

Toxic:

Acinar cells are affected first. But the mechanism of injury by alcohol and drugs is not known. Calcium activates and can increase the activation of other intra cellular enzymes.

First attack of pancreatitis occurs early in life. Family history is present. Genetic mutation is cationic Trypsinogen gene produces Trypsinogen that is resistant to Trypsin inhibitors and auto activates itself. Genetic mutation in the secretory Trypsin inhibitor SPINK 1 gene leading to inactive or defective Trypsin inhibitor

So, Trypsinogen is activated within the cell. Also seen in cystic fibrosis patients(CFTR) CFTR mutations are seen in cases of idiopathic acute pancreatitis.

Acinar cell:

It is a very active cell line. Protein synthesis producing pancreatic and zymogen enzymes are secreted by acinar cells and are assembled in rough endoplasmic reticulum which gives them their tertiary structure. Then transported to golgi complex where packaging in membrane bound vesicles occur.At the luminal end vesicles fuse with plasma lemma and

by contraction of active cytoskeleton the process of exocytosis, enzymes are released.

Lysosomal hydrolases which can activate these zymogens are secluded and separated by post translational modification of 6 mannose phosphorylation and are included in separate vesicles.

Factors preventing activation of enzymes:

Enzymes are secreted in zymogen form and are transported in membrane bound vesicles and transported along with inactivators like trypsin inactivator.

Segregation of lysosomal hydrolases which activates zymogen like cathepsin B into separate vesicles.

Changes in acinar cells in pancreatitis:

Diet induced model-Choline deficient diet with Ethionine (Lombardi et al)1975

Fusion of zymogen granules in lysosomes takes place.

Secretogogue induced model-CCK or its synthetic form Cerulin iv(lamp et al1977).

Sense defective post transcriptional modification in golgi bodies.

Ligation of Bilio pancreatic duct mode-(Seninger et al)

Here, the secreted zymogens are again taken up due to obstruction of duct into the lysosomes.Protein synthesis and secretions are normal.

Colocalisation and enzymatic activation

Pancreatic activation within acinar cells is seen in all models of pancreatitis.It is being held that intraacinar activation of enzymes is the critical event in pancreatitis leading to injury of acinar cells.Colocalisation phenomenon is still the valid hypothesis explaining enzyme activation.Some by this theory co localisation of zymogen granules and cathepsin B activates trypsinogen to trypsin and it in turn activates other enzymes.

Intracellular mediators in pancreatitis:

These include

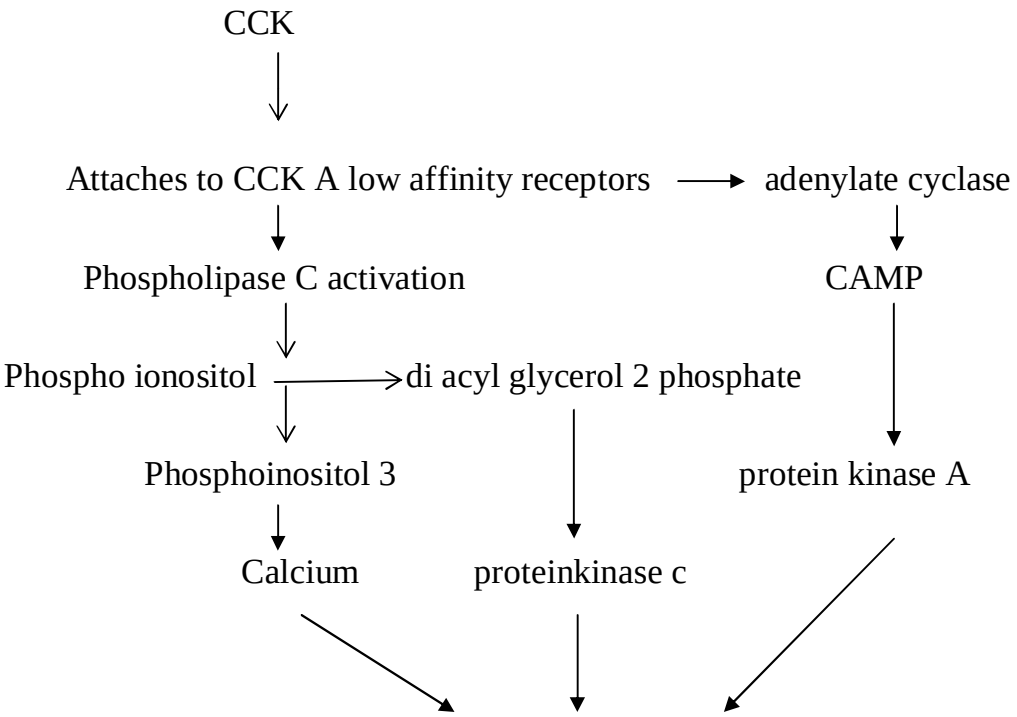
Cacium

Protein kinase c

Protein kinase a

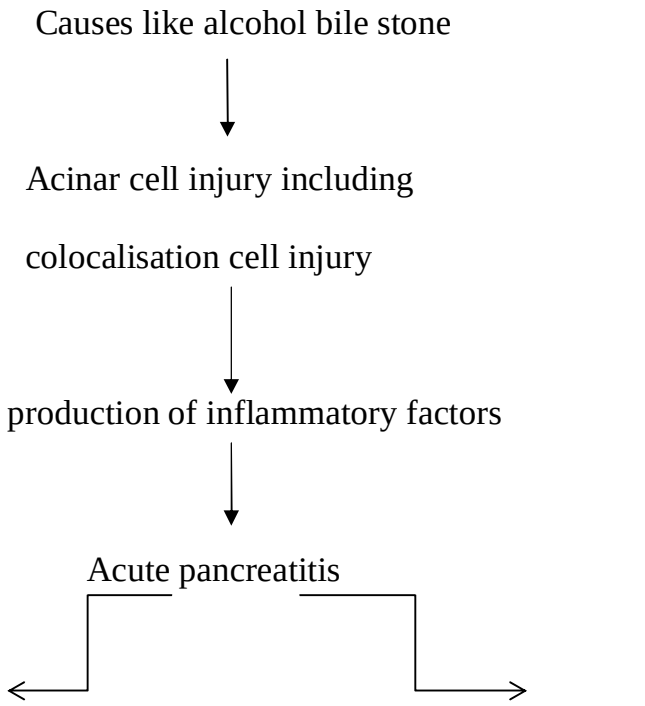
Phosphor ionositide 3 kinase

Model in CCK induced pancreatitis



1) Activation of transcription factors NFKB and
   Secretion of inflammatory mediators tyrosine kinase activation
2) PI3K leads to co localisation and enzyme activation
3) Inhibition of secretion.

Secretory determinants:



PATHOPHYSIOLOGY OF ACUTE PANCREATITIS

Three important events in pathophysiology of acute pancreatitis are,

Changes in circulation of pancreas

Inflammatory response(both local and systemic)

Increase in permeability of gut.

Changes in circulation of pancreas

Changes are,

Vasoconstriction

Capillary stasis

Oxygen saturation decreases

Ischemia

Reperfusion injury plays an important role in the pathogenesis of pancreatitis. Reperfusion causes vasodilation and initiates production of oxygen free radicals.

The balance between nitric oxide and endothelin is an important determinant and the induction of **inducible Nitric oxide Synthase** may be a therapeutic target in patients with pancreatitis.

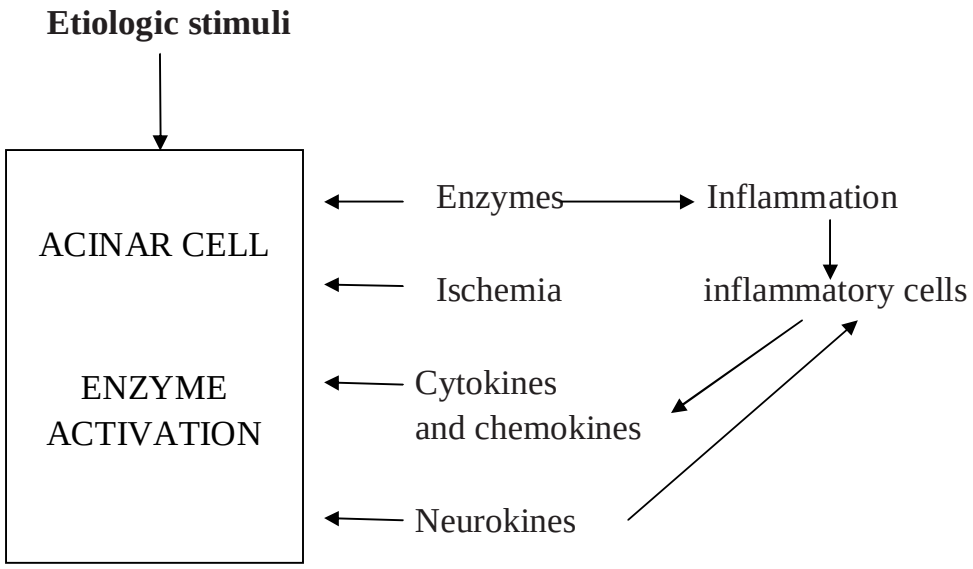
AMYLIN

Amylin is a polypeptide secreted by beta cells causes hypoperfusion to exocrine areas in pancreas and it’s values are elevated in setting of acute pancreatitis.

RENIN ANGIOTENSIN SYSTEM

Renin angiotensin system also has been found to be upregulated in pancreatitis,but the value of angiotensin inhibitors in pancreatitis in underway in experimental trials.

Local and systemic inflammatory response



Acinar cells that are injured by the etiologic stimuli creates oxygen free radicals that destroys other cell's membrane and leads to the release of chemoattractive substances.

This is proved by the finding of increased levels of oxygen free radicals and antioxidants(like beta-carotene).

Next step is the **migration of leukocytes** into the region of inflammation and is brought about by adhesion molecules like ICAM-1, which is a powerful agent for attraction of neutrophils.

Neutrophils are the first cells to enter the field and their product **PMN elastase** is increased as one of the earliest markers in acute pancreatitis.

Neopterin is also raised but it is a late marker as it is secreted by macrophages which reach the field late in the course of disease.

Cytokines

Cytokine release is the next step in the inflammatory reaction and they are secreted by different types of cells and are chemically low molecular weight proteins.

They have pleotrophic functions and act on different types of cells and many of them share their biological functions.

Different cytokines that are elevated in pancreatitis and thereby,can be used as markers of severity are,

Tumor necrosis factor-alpha
IL-6
IL-1receptor antagonist
IL-10

TNF-alpha

TNF-alpha is a early marker of severity but is cleared rapidly by the liver. So instead, TNF-a receptor is used for this purpose.

IL-1

IL-1b is a mediator for inflammation raises along with it's receptor and it's converting enzyme which cleaves it to it's active form.

IL-6

IL-6 is secreted by different types of cells like macrophages, monocytes , smooth muscle and endothelium.

It is one of the early severity marker for pancreatitis and it's elevation correlates with that of Phospholipase A2.

It is the main stimulus for the production of acute phase proteins in the liver and so is elevated before the levels of C-reactive protein.

IL-10

IL-10 is anti-inflammatory and is so protective in acute pancreatitis.It increases in the first 24 hrs and has a steady decline thereafter.

HGF-

Hepatocyte growth factor is a Organotrophic factor that prevents apoptosis of cells and thereby protects the pancreatitis.

PAF-

Platelet activating factor activates platelets,and increases endothelial permeability and thereby leads to hypotension, hypovolemia and ischemia of organ systems.

It is released by the action of Phospholipase A2 on the cell membranes.

It has been found as the therapeutic target for patients with acute pancreatitis.

The level of cytokines that correlate with the incidence of Multiple organ dysfunction syndrome (MODS).

GUT PERMEABILITY IN PANCREATITIS

Intestine also has a role in pathogenesis of pancreatitis and occurs at 72 hrs from the symptom onset.

Low intramucosal PH in bowel shows the damage occured to the intestinal mucosa and denotes intestinal mucosa and it correlates with

parenteral nutrition and malnutrition specifically to the gut mucosal cells.

Microscopically, reduction in height of villi and low mast cell number is seen in small intestine in cases of pancreatic necrosis.

This leads to the translocation of bacteria occurs through the intestinal mucosa and is responsible for the infection of the pancreatic necrosis.

Different studies hold different opinions in whether translocation of endotoxins or bacteria occurs.

\SYSTEMIC INFLAMMATION

In necrotising pancreatitis,due to acinar cell damage leakage of cytokines occur that enter the general circulation and leads to the syndrome of SIRS ending in the failure of organ systems called Multiple organ dysfunction syndrome.

Definition for systemic inflammatory response syndrome

Any two of following criteria amounts to SIRS,

Rectal temperature > 38°C or < 36°C

Heart rate > 90 bpm

Respiratory rate > 20 breaths/min or *P*aCO2< 32mmHg

White blood cell count > 12 000/cu.mm or < 4000/cu.mm or 10% immature cell forms.

Definition of Sepsis

Infection and associated Systemic inflammatory response syndrome

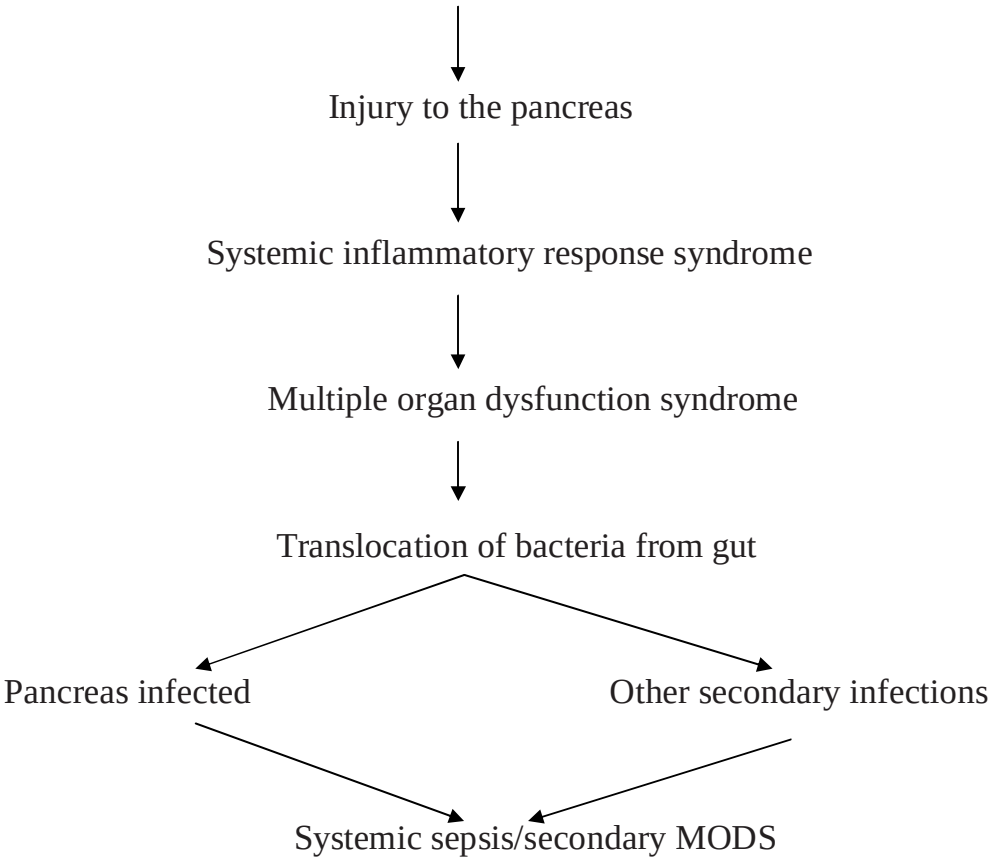
Definition of Severe sepsis

Hemodynamic compromise and sepsis

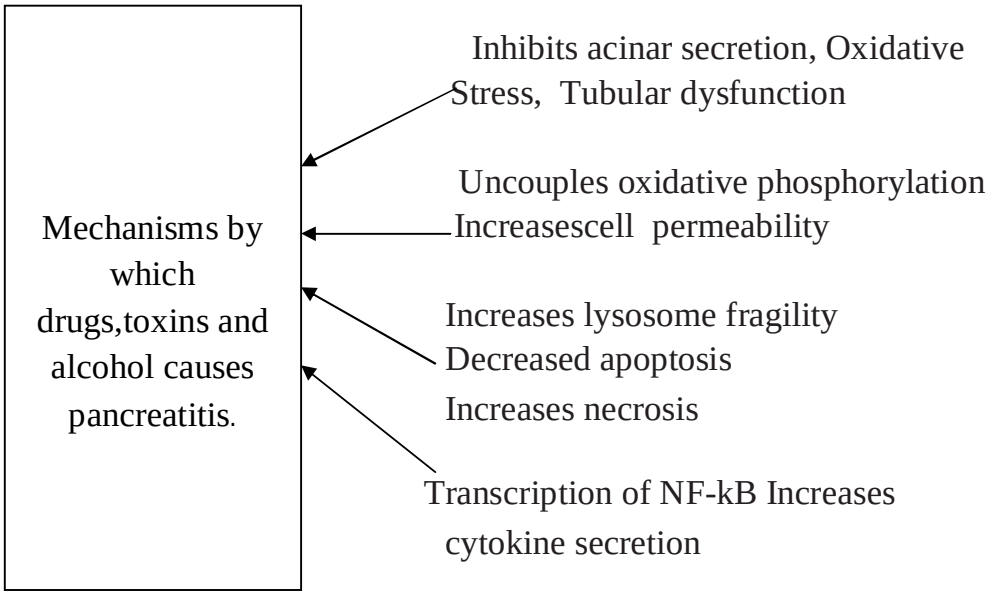
Definition of multiple organ dysfunction syndrome

Failure of more than one organ system with inability to sustain homeostatic mechanisms.

Development of MODS



PATHOPHYSIOLOGY OF ALCOHOLIC AND TOXIC PANCREATITIS



CLINICAL FEATURES:

Acute pancreatitis is equally common in men and women,but uncommon in children. Mostly occurs in elderly patients in their sixth decade of life. Epigastric pain with sudden onset increasing in severity, boring in character, radiating to back with patient taking a leaning forward posture is classical of pancreatitis. Vomiting may be present.

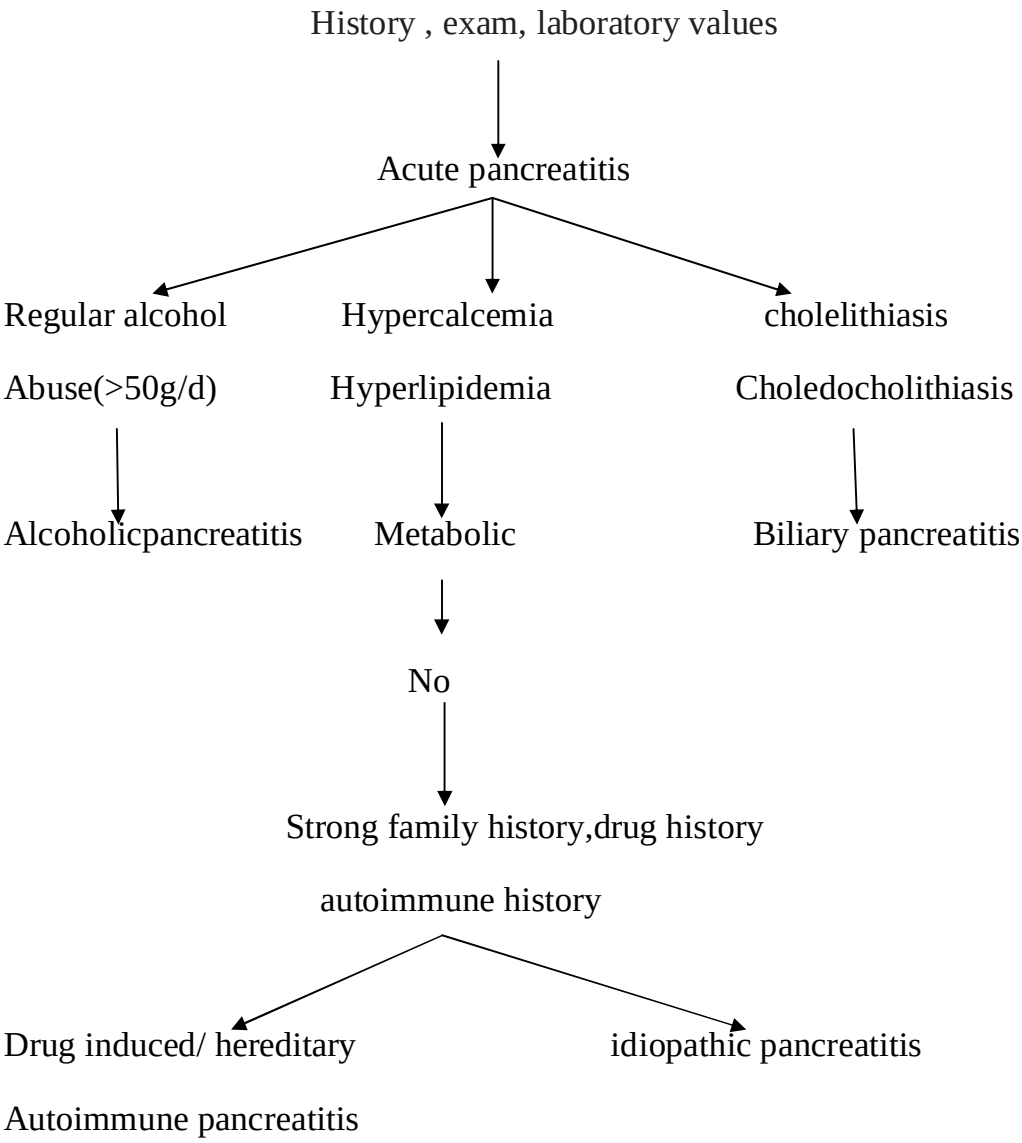
Clues to etiology include an alcoholic binge before the onset of pain being a marker to alcoholic pancreatitis, jaundice, if present indicates gall stone pancreatitis and positive family history of pancreatitis is towards a hereditary pathology.

Patients in severe end of the spectrum have multiple organ dysfunction syndrome or systemic inflammatory response syndrome. These patients present with high fever, altered mentation,shock and Acute respiratory distress syndrome(ARDS). Ecchymotic lesion in the umbilical region is called CULLEN'S SIGN and in the flanks is GREY TURNER'S SIGN are uncommon and are seen in hemorrhagic pancreatitis.

These signs are seen only in 3-5% of cases but when seen are associated with 35% mortality.

OTHER SIGNS

Eye signs are Arcus lipoides in hyperlipedemic cases of pancreatitis,Band Keratopathy in hypercalcemia, rarely retinal examination shows Purtscher's retinopathy.Panniculitis(subcutaneous fat necrosis) and polyarthritis can be seen in autoimmune cases.


History , exam, laboratory values
Acute pancreatitis
Regular alcohol
Abuse(>50g/d)
Hypercalcemia
Hyperlipidemia
cholelithiasis
Choledocholithiasis
Alcoholicpancreatitis
Metabolic
Biliary pancreatitis
No
Strong family history,drug history
autoimmune history
Drug induced/ hereditary
Autoimmune pancreatitis
idiopathic pancreatitis

DIAGNOSIS OF PANCREATITIS

Laboratory investigations can support the diagnosis of acute pancreatis. Radiology investigations can confirm the diagnosis.

SERUM AMYLASE

Serum amylase (1,4-a-D-glucan glucanohydrolase) is a digestive enzyme secreted from acinar cells that breaks the internal alpha-1,4 bonds in sugars during digestion.

Due to inflammation of the gland, secretion of amylase into pancreatic juice is defective leading to leak of the enzyme into the surrounding parenchyma and gets absorbed into circulation.

Levels start to rise after 2 hours, peak levels are attained at 48 hours, and fall to baseline in 4 to 5 days.

Serum level of amylase has no bearing in finding the etiology of AP and it also correlate with the severity of the disease.

Limitations are,

1 If done after days of the initial inflammation, it might have fallen back to the baseline values.

2 Hypertriglyceridemia, if present as the cause, secretes a inhibiting substance that prevents the raise of amylase levels in which case serial dilutions of the test is needed.

3 In alcoholic Pancreatitis,due to damage of the acinar cells amylase secretion is defective.

Causes of Increased Serum Amylase Activity

Other Pancreatic diseases

Acute pancreatitis(all types and etiologies)

Pancreatic cancer

Abdominal emergencies

Acute Cholecystitis

Common bile duct obstruction

Perforated viscous

Intestinal ischemia

Acute appendicitis

Ruptured ectopic pregnancy and acute salpingitis

Salivary gland diseases

Renal insufficiency

Macroamylasemia

Diabetic ketoacidosis

HIV infection/AIDS

Sphincter Oddi stenosis or spasm

Drugs: Morphine

Specificity of the test is only 88% due to presence of other causes of amylase elevation,but it is raised to 90% when the level is more than three times normal.

Isoenzymes of Pancreatic amylase (p-isoamylase) normally raises in acute pancreatitis to more than three times normal.

It has 90% sensitivity and 92% specificity.But increased levels of p-isoamylase is also seen in intestinal perforation,renal failure and ketoacidosis in diabetes.

Amylase/C reatinine clearance ratio is elevated to upto 10% from its normal value of 3% in acute pancreatitis, but this test is also not specific to AP,but it can be useful in differentiating macroamylasemia where urinary excretion of amylase is not elevated.

SERUM LIPASE

Serum lipase (Triacylglycerol Acylhydrolase) is also a product of acinar cells which breaks glycerol esters in fatty acids during digestion.

Values of lipase increases 6 hours of inflammation and reaches its peak at 24 hours but remains there for 8-13days after which it starts to decline .

Sensitivity and specificity of lipase are 94% and 96% respectively if the values are 2 to 3 times normal.

It can also be seen in other causes but is more specific than amylase in diagnosing pancreatitis.

Those conditions with Hyperlipasemia are,

Peptic ulcer disease

Small bowel obstruction

Hypertriglyceridemia

Diabetic ketoacidosis

Renal insufficiency.

Crohn’s disease

Autoimmune diseases like Sarcoidosis

COMBINED AMYLASE AND LIPASE

Combined Amylase and lipase estimations has failed to increase the accuracy than both the tests done alone. However it is being done often in clinical setting. A serum lipase level and/or with radiology investigations can give the diagnosis in 32% of patients with normal amylase levels and pancreatitis.

TRYPSINOGEN

Trypsinogen (25-kDa pancreatic protease) is also secreted by pancreas and has two isoforms 1 & 2. Trypsinogen-2 is elevated in both blood and urine upto 12 fold.

Sensitivity and specificity are 93% and 95.5% respectively, but the negative predictive value is almost 100% and so a negative test rules out the disease.The test is yet to be validated in international trials.

Other upcoming tests for diagnosing AP are,

Serum immunoreactive trypsin,

PMN elastase

Chymotrypsin

Phospholipase A2

Pancreatic activated protein(PAP).

Alpha 2-macroglobulin

COMPLICATIONS OF ACUTE PANCREATITIS

Severe Acute Pancreatitis

According to the Atlanta classification,severe pancreatitis is defined as presence of local complications or systemic complications like Organ failure.

Fluid Collections

They are situated near the pancreas or in the substance of pancreatic parenchyma.They may develop into pseudocyst or may get infected to form an abscess.

Necrotising Pancreatitis

Due to ischemia,the area of pancreatic parenchyma becomes nonviable and forms area of necrosis.By definition, it should be more than 3cm in imaging studies.

Pancreatic Abscess

It is the collection of pus in and around the pancreas in the retroperitoneum and it may or maynot contain necrosis.

MODS and Organ failure

It may de defined by the presence of hemodynamic compromise,(Systolic BP-less than 90 mmhg),ARDS with PaO2 < 60 mmhg,Renal failure requiring dialysis or creatinine >2 or severe GI bleed.

RADIOLOGY IN ACUTE PANCREATITIS

The use of radiology in acute pancreatitis is to

to confirm the diagnosis

to identify the possible etiology of pancreatitis(eg,biliary)

to assess the grade and local complications.

Ultrasound

It is usually not used as primary mode of imaging (due to poor imaging of pancreas because of intervening bowel gas) in acute pancreatitis other than cases with suspicion of biliary etiology for pancreatitis where gall stones can be ascertained by ultrasonography.

Findings are,

Hypoechoic gland or parts of gland

Edematous or enlarged gland

Pancreatic ascites

Areas of hemorrhage and necrosis

Computed tomography

It is the most important radiographic investigationin the diagnosis of pancreatitis and it also rules out other causes of acute abdomen like hollow viscus perforation and other inflammatory conditions.

It also helps in grading the disease thereby gives the severity of the diseaseand identifies the complications.

Findings that are suggestive of the diagnosis are,

Enlargement and edema of the pancreas

Heterodense parenchyma

Peripancreatic fat stranding

Obliteration of fat planes around the pancreas

Peripancreatic and extrapancreatic fluid collections.

A focal or diffuse area of nonenhancing portion of parenchyma on examination with oral and i.v contrast is the classical finding for pancreatic necrosis in CT examination.

Magnetic resonance imaging

MRI with the advanced technology of Magnetic retrograde pancreaticocholangiography is more extensively used in pancreatitis but its utility in acute pancreatitis is minimal.

MRCP detects severity of pancreatitis and is equivalent to CT severity index in this regard. It can also give pancreatic necrosis as good as a CECT.

It is superior to all modalities in

Pancreatic duct changes and anatomy

Gall stones and CBD stones.

It can be used in patients with renal insufficiency where CECT cannot be used as Gadolinium,contrast used in MRI is not nephrotoxic.

Endoscopic retrograde cholangiopancreatography

It has no role in acute pancreatitis except being used to remove CBD stones with sphincterotomy and to delineate main pancreatic duct anatomy in unresolved and recurrent pancreatitis cases.

ASSESSMENT OF SEVERITY IN ACUTE PANCREATITIS

BACKGROUND

In clinical setting, acute pancreatitis shows great variations. Majority of patients have a self limiting and mild disease(85%) and they need only general therapy and can be treated in surgical wards. The remaining 15% patients have either local or systemic complications and the disease is frequently fatal due to multiple organ dysfunction syndrome.

In 1992 an expert group in the Atlanta classification gave the definition for severe cases in pancreatitis as failure of one or more organs and/or locally complicated disease with pseudocyst, nacrosis or abscess.

These patients will need continuous monitoring in a intensive care unit and may need surgery like necrosectomy for pancreatic necrosis or abscess drainage in pancreatic abscess.

From 1970s since ranson devised his prognostic scoring system in pancreatitis,the past four decades have seen multiple comparison studies between scoring systems (clinical,biochemical ,radiologic) through multiple studies.

Definitions in acute pancreatitis given by Atlanta classification in 1992 have been widely accepted and has increased the accuracy of evaluating the different prognostic markers against each other.

From the understanding of pathophysiology of acute pancreatitis, it is known that only the initial phase of the disease is caused by enzymes released and after 72 hrs, the disease becomes a systemic inflammation and is independent of initiating the disease and causes SIRS and MODS.

So, treatment modalities instituted before 72 hrs of initiation can have significant effect in improving the morbidity and mortality rates.

Therapy measures that could be advantageous if started early, within 72 hrs include,

1. antibiotic prophylaxis in infected necrotic pancreatitis
2. early enteral nutrition could reduce complications when compared to parenteral nutrition.
3. endoscopic sphincterotomy may help patients with gallstone pancreatitis
4. immunomodulators and cytokine inhibitors may have a role.

CLINICAL SCORING SYSTEMS

Some clinical signs if present may indicate worse prognosis like,

Fever

Tetany

Palpable abdominal mass

Cullen’s sign and Grey Turner’s sign

Pleural effusion

These are not specific enough to predict severe acute pancreatitis and so scoring systems are sought.

Ranson score and Glascow score are the multivariable models where 8-11 different variables are assessed.the main difference between the two is that Ranson's score is described mainly for alcoholic pancreatitis whereas, glascow's score is effective in pancreatitis due to all etiology.

Limitations of these scoring methods

1.Score can be given only after 48hrs after two serial values of the variables are assessed which is the golden hour in acute pancreatitis when treatment if instituted are effective.

2.these scores have high negative predictive value(90%) but poor positive predictive value(40-50%) and so they can only be used to rule out patients who donot have severe disease.

3.there is no followup criteria and so course of the disease cannot be studied.

Ranson's scoring system for the prognostic evaluation of acute pancreatitis.

Severe pancreatitis is defined by the presence of three or more criteria.

At admission
Age > 55 years
White blood cells > 16 000/mm3
Lactate dehydrogenase > 350 U/L
Aspartate aminotransferase > 250 U/L
Glucose > 200 mg/dL

Within 48 hour
Hematocrit decrease > 10%
Blood urea nitrogen increase > 5mg/dL
Serum calcium < 8mg/dL
*P*aO2 < 60mmHg
Base deficit > 4 mEq/L
Fluid sequestration >6L

Glasgow scoring system for the prognostic evaluation of acute pancreatitis during initial 48 hours.

Severe pancreatitis is defined by the presence of three or more criteria.

White blood cell > 15 000/mm3
Glucose > 10 mmol/L (no history of diabetes)
Serum urea > 16 mmol/L
*P*aO2 < 60mmHg
Serum calcium < 2.0 mmol/L
Aspartate aminotransferase/alanine aminotransferase > 250 U/L
Lactate dehydrogenase > 600 U/L
Albumin < 3.2 g/dL

APACHE II SCORE

APACHE II (acute physiology and chronic health evaluation score II)score was originally designed to give the possibility of death in ICU setting due to variety of diseases.

It can be calculated at admission and so is more useful than ranson’s score. But, it also has low positive predictive value like the previous scores.

An increasing score may indicate severe disease and declining values indicate mild disease since serial scoring is possible.

Obesity is found to have deterrant effect on course of the disease and so BMI(body mass index) is added to the score recently and the score is called **APACHE-O score.**

BIOCHEMICAL MARKERS OF SEVERITY.

Protease activation-markers.

Activation of proteases happens in acute pancreatitis in early steps and activation of trypsinogen occurs to form trypsin which activates other proteases like

PhospholipaseA2

Procarboxypeptidase B

During activation of proteases, a peptide moiety is released from the enzyme and is called Activation peptide.It’s level measured in blood and urine gives the local damage to the gland and thereby,the severity of the disease.

TAP-trypsinogen activating peptide

It reaches it's peak level at 24 hrs and falls to baseline quickly within 3 days which restricts it's utility in prognostifying the disease.

This test has inconsistent sensitivity and specificity in multiple studies and presently can be used only in cases within 24 hrs.

CAPAP-Procarboxy peptidase activation peptide.

It is more stable easy to measure than TAP,but it also falls very rapidly and the test can be used only in the first 24-48 hrs.

PLAP-phospholipase activation peptide

This could be useful marker in the future because, it is released both pancreas and granulocytes and so can give the measure of both events of pathogenesis-enzyme activation and inflammatory reaction.

Inflammatory reaction-markers

In all types of pancreatitis, secondary event in pathogenesis is inflammation which releases cytokines and other mediators like oxygen free radicals and interleukins(IL-8).

These lead to attraction of polymorphonuclear cells and macrophages/lymphocytes and they release more cytokines and proteases.If excessive stimulation of inflammatory mechanisms occur,SIRS ensues.

Major mediators of inflammation that are studied as markers of severity are,

Tumor necrosis factor(TNF)

IL-6 and IL-8

PMN elastase

C-reactive protein(CRP)

These are essentially nonspecific to pancreatitis and are markers of inflammation.

PMN elastase

This marker is positive even on the first day of disease and starts falling after 48 hrs and it’s value in severity is on the first day of pancreatitis.

It has high sensitivity and specificity of 85-95% and is measured by immunoagglutination.

Interleukins

They also increase within 24 hrs and so is first day marker of severity in acute pancreatitis

TNF(Tumor necrosis factor)

It is known that TNF is released in a inconsistent and intermittent way and so serum levels of soluble TNF receptors have become test to differentiate mild from severe disease.

It reaches specifically high levels in patients develop organ failure.

CRP-C reactive protein

It is the most widely available and cost effective marker and is synthesized in the liver by action of IL-6 and IL-1. Serum levels rise slowly and reach peak values between 48-72 hrs.

Serum levels more than 100mg/dl-150mg/dl is considered positive.

Sensitivity and specificity are more than the clinical scores,but is lower than Interleukins and PMN elastase.

It also predicts necrotising pancreatitis with high sensitivity.

It can also function as a marker used to decide on the necessity of contrast enhanced CT scan.

Inspite of all these considerations, CRP reaches it’s peak at only 48-72 hrs and so cannot determine the severity in the therapeutic window of pancreatitis(first 72 hrs).

Imaging in severity assessment

CTSI:

CT is the most efficient and reliable method for evaluating patients with acute pancreatitis. It is justified in doing CT in acute pancreatitis because it can confirm the diagnosis as well it can give early assessment os disease severity.

It can also be use to detect and follow up life threatening local complications and it can rule out other disorders presenting like acute pancreatitis.

Oral contrast agent is given just before scanning and IV non ionic contrast 3-4 ml/sec bolus injection. CT acquisition starts after 60 s of IV contrast injection.

Helical CT with 5 mm axial collination –two phase acquisition technique- arterial and portal venous phase is used.

Normal pancreas- 40 to 50 HU

Arterial phase- 150 HU

Portal phase- 100 HU

Normal variation 10-20 HU can be there.

In acute pancreatitis, small ill defined heterogenous collection develop , with 20 -40 HU attenuation values and represents a combination of inflammatory exudate, fat necrosis and haemorrhage.

Diseased pancreas failed to enhance during IV contrast administration and it is the most and consistent and distinguishing feature of ischemia and and pancreatic necrosis and is the classical CT feature to give the necrosis and therby severity of outcome and protracted clinical course.

It is known that pancreatic necrosis is directly related to mortality 2- 10% and recently it is found to be the phenomenon occurring at the beginning of acute attack rather than being the end result of severe panctreatitis and thus have become one of the grave prognostic indicator of outcome in patients with acute pancreatitis. The first CT based grading was based on plain CT imaging and gave mortality and morbidity of 14% and 54% for D and E and no mortality and 4% morbidity for A,B,C.

Balthazar and Ranson's CT severity Index

Description	Score
Pancreas normal	0
Enlarged gland,necrosis less than 3 cm, fluid collection in the pancreatic parenchyma	1
Inflammatory changes ,peripancreatic changes	2
Fluid collection around the pancreas(single)	3
Multiple collections around pancreas or abscess formation	4

Necrosis	Score
None	0
<30%	2
30-50%	4
>50%	6

DEMERITS:

Plain CT could not give pancreatic necrosis as no contrast enhancement was used.

Inability to predict morbidity in fluid collection most of which resolved spontaneously but are given as high grade in plain CT index.

CTSI: included IV contrast enhancement and incorporated necrosis score in the total CTSI score patients with normal enhancing pancreas 0% mortality and 6% morbidity, but those with areas of necrosis had 82% morbidity and 23% mortality.

	Morbidity	**Mortality**
0-2	4	0
3-6	35	6
7-10	17	92

Limitation of CTSI:

Most of them are due to poor techniques, motion artifacts, lack of iv contrast administration and poor quality studies.IV contrast cannot be given in allergic patients and renal failure.

Early necrosis, ischemic finding at 2-3 days are hard to find and so all patients with suspicious and equivocal findings and with large pancreatic and peri pancreatic collection should undergo repeat CT scan as follow up.

Pancreatic exudate extravasated can obscure the changes in retroperitoneum and can present even without recognised changes in pancreatic parenchyma and may need a needle aspiration to differentiate.

TREATMENT GUIDELINES IN ACUTE PANCREATITIS

CONSERVATIVE MANAGEMENT

Supportive care

Fluid replenishment is the cornerstone of treatment to correct hypovolemic shock and other third space losses.

Supplemental oxygen should be given during first day to all cases and specially to patients on opiods for pain control.

Analgesia should be adequate.

Nil by mouth to provide bowel rest is important and the interval after which oral diet can be resumed is controversial and is a topic of

undergoing trials, most of which suggest early enteral feeding to prevent changes in intestinal mucosa and thereby bacterial translocation.

Treatment in intensive care unit

Patients who need transfer to an intensive care unit are,

a. Those with sustained hypotension and decreased oxygen saturation and who doesnot respond to a bolus of i.v fluids.

b.Patients with evidence of renal failure.

c.Older patients with cardiac disease and patients with respiratory fatigue.

d.Patients who need continuous monitoring like patients on pressor support and those who need dialysis.

Nutrition

Simple dictum is all patients who are nil per mouth for a week will need nutritional support.

Enteral feeding is better than parenteral mode due to following reasons.

It prevents complications caused by TPN like hyperglycemia and septicaemia.

It also prevents intestinal mucosal injury and thereby translocation of bacteria from the gut.

Nasogastric tube feeding is found comparable to nasojejunal tube feeding and is now advised as mode of enteral nutrition.

Role of prophylactic antibiotics

Even if it is associated with organ failure,interstitial or edematous pancreatitis doesnot show changes in morbidity and mortality with prophylactic antibiotics.

But in cases of necrotising pancreatitis, all the six studies done show improvement in mortality with prophylactic antibiotics and decreased rate of infection of the pancreatic necrosis.

With the increasing use of antibiotic of wide spectrum like carbapenems,fungal infection of pancreatic necrosis is on the rise.

Infected necrosis-management

It is known that if infected necrosis is suspected either by,

First 7 days-fever and leucocytosis

From 7-15days-if fever and leukocytosis persist or if organ failure persists beyond that time.

Infected necrosis is diagnosed by,

Ultrasound or CT guided aspiration for gram staining and culture.

Reasons in support of aspiration are,

It can give sensitivity of the organisms and so appropriate antibiotics can be instituted.

Since the prevalence of fungal infections is on the rise, broad spectrum antibiotics should be avoided in patients with negative staining and culture.

It has been advocated that surgical necrosectomy is indicated in all patients with infected pancreatic necrosis which has been questioned in the latest studies which advocate only antibiotics in the acute phase in infected necrosis.

This can allow the infection to settle and a more definitive single stage procedure can be done in these cases.

Alternatives to surgical necrosectomy in these cases are,

Minimally invasive necrosectomy

Percutaneous catheter drainage, by multiple radiologically placed catheters.

Pancreatic abscess is defined as the liquefaction and infection of already and secondary infection of a residual area of necrosed area of pancreas or infection of a pseudocyst around the pancreas and it is mostly treated by percutaneous drainage.

Sterile necrosis-management

In cases with sterile necrosis, early intervention in the first 2-3 weeks has been found to be a method to decrease the occurrence of organ failure and outcome in patients with fever, leukocytosis and organ failure.

But otherwise in patients with sterile necrosis, early necrosectomy has been found to have negative consequences in the morbidity.

So, it is wise to wait atleast 3 weeks to allow the peripancreatic inflammation to settle and to allow a onestage necrosectomy.

Both percutaneous drainage in cases of necrotic collections and surgical procedures like cysto-gastrostomy and cysto-jejunostomy in cases of pseudocyst formation may be needed.

Pancreatic duct damage-treatment

It may be complete rupture of the duct-disconnected duct syndrome or partial rupture.

It is suggested by increase or persistence in size of collection in CT scan.

Treatment-

If no symptoms-no treatment

If symptoms are present-increasing pain-ERCP done to document duct damage and treatment is by nasojejunal feeding and Octreotide (to decrease pancreatic secretions and to allow healing of the damaged duct.

Endoscopic stent placement is usually unsuccessful.

Biliary pancreatitis-role of sphincterotomy

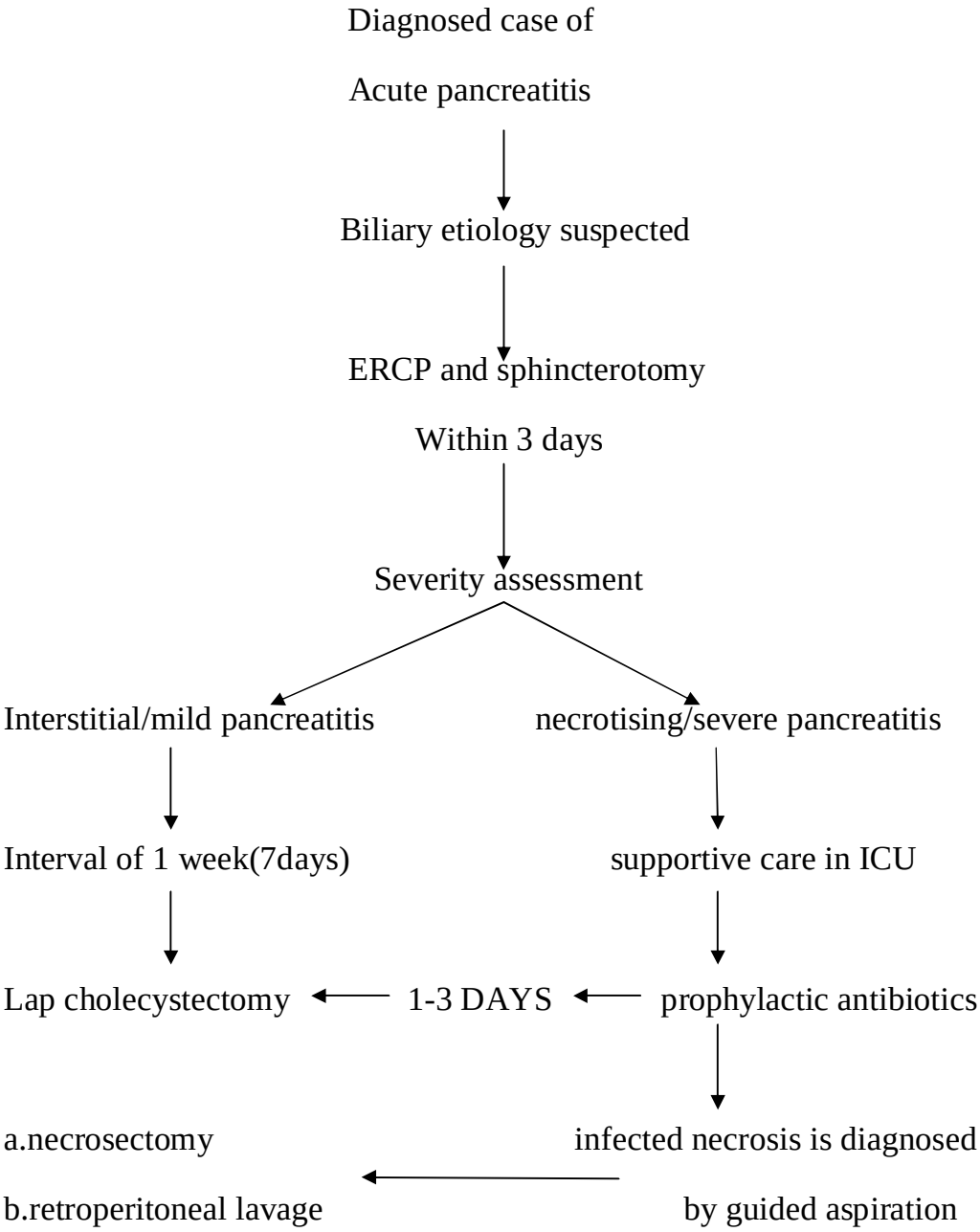
It should be done early in the course of disease to be useful and should be within 1 or 2 days.

Patients who have early signs of organ failure are the most benefitted group from sphincterotomy.

It is useful mostly due to preventing ascending cholangitis which is the reason for organ failure.

Sphincterotomy is useful due to the removal of Common Bile Duct stones.

TREATMENT ALGORITHM FOR BILIARY PANCREATITIS



INDICATIONS FOR SURGICAL TREATMENT IN ACUTE PANCREATITIS

a. Infected pancreatic necrosis

b. when the diagnosis is uncertain

c. associated gall stones or CBD stones

d. if patient's condition deteriorates inspite of supportive care.

Diagnosis is uncertain

In some cases diagnosis of acute pancreatitis cannot be ascertained inspite of good clinical exam and laboratory tests. CT is of great help in those cases.

But in some rare cases, where diagnosis is uncertain, exploratory laparotomy is done mainly to rule out surgically correctable disease.

In these cases, after ruling out other causes of acute abdomen,

Sample of peritoneal fluid for amylase, lipase, cell count and culture is taken.

Pancreas is visualised-if found normal, left undisturbed.

In cases of noninfected pancreatic necrosis with exudates, a peritoneal dialysis catheter is left in the peritoneum in view of giving peritonel lavage post operatively.

Infected pancreatic necrosis

As already seen,

A circumscribed collection of purulent material around the pancreas is pancreatic abscess.

Infected pancreatic necrosis is patchy or diffuse areas of nonviable parenchyma in the pancreas.

Infection occurs by,

Bacteria from the colon through transmural route

Bacteria from the duodenum or biliary system

Hematogenous spread

Organisms are,

Enterococcus

Klebsiella

E.coli

Anerobes and fungi

polymicrobial

High suspicion is needed to diagnose infected necrosis,that too it should be sought in all cases with deteriorating clinical status.

It cannot be diagnosed by any radiologic means, except in some rare cases where air is seen in the pancreatic area and adjacent retroperitoneum.

The only confirmatory test is guided aspiration and staining/culture.

If percutaneous drainage fails, surgery is indicated,

a. necrosectomy with open packing
b. necrosectomy with closed drainage
c. necrosectomy with continuous lesser sac lavage.

Debridement should encompass only already necrosed and degraded tissue as excess of debridement may cause hemorrhage that is troublesome.

Associated Biliary disease

Approach to biliary pancreatitis was to wait for 2 months after an episode of acute pancreatitis.

But this approach has lost it’s favour because frequent recurrences occur after the initial episode and so nowadays, cholecystectomy with or without CBD exploration and cholangiography is done safely after 3-6 days with classical open approach or minimally invasive method.

Before elective cholecystectomy, rate of recurrence of pancreatitis is 45-55%,but after surgery it is reduced to 5%.

If suspicion of CBD stones exist, preop ERCP is done in view of sphincterotomy and removal of stones.

Exception to this rule is ,

Severe Biliary pancreatitis patients whose clinical course is prolonged but who are improving with signs of,

a. Paralytic ileus

b.Fluid collections

c. ascites

In these patients, it is wiser to do a interval cholecystectomy after 4 weeks.

Worsening clinical status

These patients fail to respond to conservative measures and there clinical status is deteriorating.

It has been proved beyond doubt that,debridement and pancreatic resection in these patients with no evidence of infected pancreatic necrosis or biliary obstruction increases the mortality rates.

Therefore, conservative supportive measures are the line of treatment in these patients currently.

CRP:

Acute phase proteins are systemic response to inflammation and it is mediated by cytokines, **Baumann** and **Gauldie** 1994.

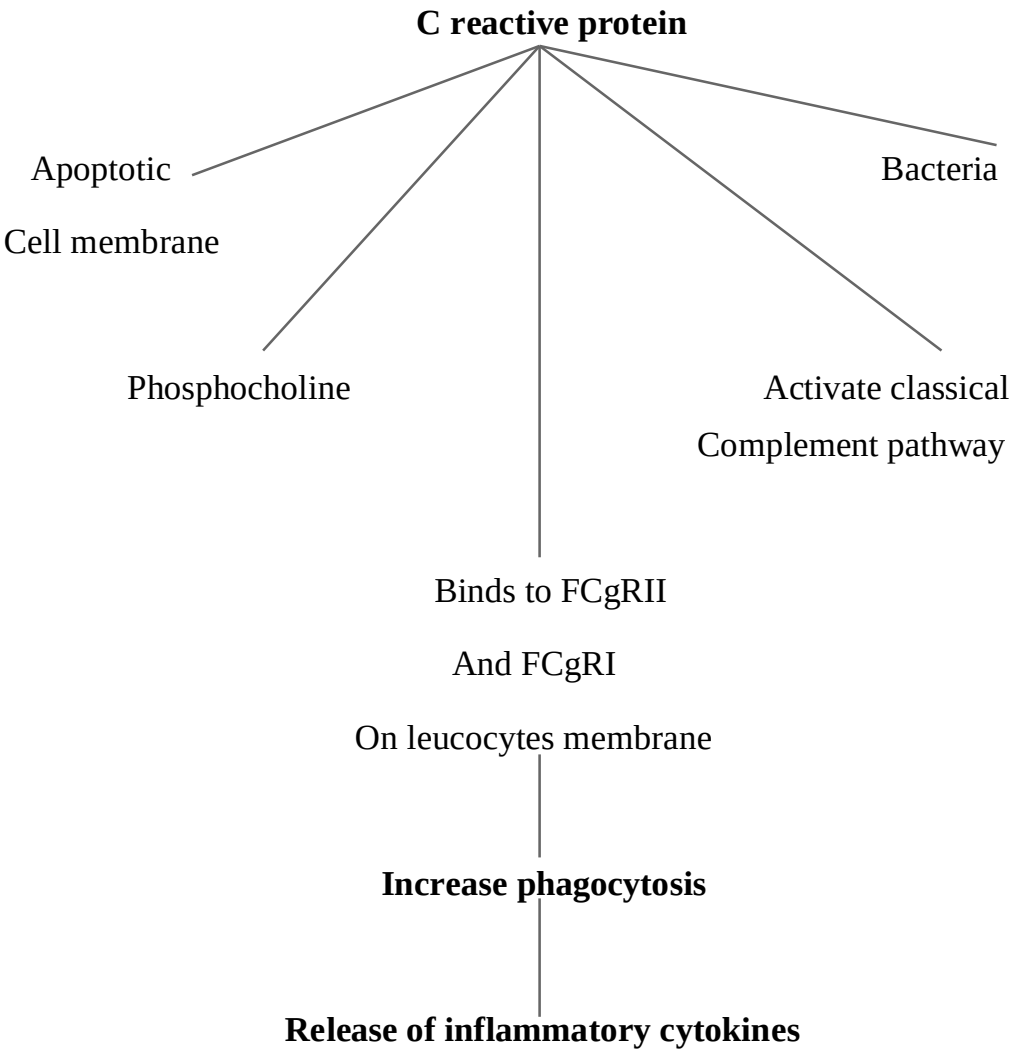
C reactive protein, discovered by Francis and **Tillet**, 1930 is one of the acute phase proteins. Named so because it agglutinates some members of Pneumococcus species binding to the C polysaccharide.

It was identified by **Abernethy** and **Arey** in 1941 as protein crystallized by Mc carty 1947 and Anderson and Maccarty in 1950 gave its medical applicability in Rheumatic patients to find Rheumatic activity.

It belongs to the Pentraxin, protein family with a calcium dependent ligand function . its electron microscope picture was given by Osmand et al in 1977as containing five identical subunits arranged in pentagon ring structure.

Liver is the major site of production of CRP and other acute phase proteins (Kushner and Feldman 1978). The major inducing cytokine is IL 6(Castell et al 1989).Interleukin and TNF alpha are not independent inducers of CRP synthesis but modulators(Kushner et al 1987, Taylor et al 1989).

IL 6 is mainly induced by monocyte macrophage granular leucocytes and many other types of cell and what makes it specific as the marker of inflammation is till now no specific pro inflammatory stimulus has been found for secretion of CRP by liver.



Function of CRP could seem to be to provide

1. Non specific innate immunity by protection against harmful foreign molecules .

2. Restoration of normal structures a function by clearance of injured apoptotic and necrotic host cells.

CRP is the single commonly used marker in severity in pancreatitis and it is a measure of hepatic acute phase response (Wilson et al 1989).

Peak levels of CRP are reached only after 48-72 hours of the start of inflammation and so its role is limited in early disease but it is useful in follow up of disease (Neptolemos et al 2000, Puolakkainen et al 1987).

CRP is also elevated in conditions like

Coronary heart disease,

Insulin resistence,

Diabetes,

Dental disorders,

Smoking,

Over weight,

Obesity,

Alzheimers disease,

Rheumatois arthritis,

Cancer.

PATIENTS AND METHODS:

50 Patients admitted to emergency ward, Stanley medical college hospital, Royapuram Chennai from June 2011 to October 2012 diagnosed as acute pancreatitis (ethanol induced) are selected for the study, after through history which includes history of alcohol intake), clinical examination and basic laboratory investigations.

Diagnosis of acute alcoholic pancreatitis is made by,

Acute onset of epigastric boring pain radiating to the back with history less than a day and absence of previous history of similar pain.

History of intake of alcohol is asked and patients affirmed are included.

Biochemical confirmation by serum amylase (>4 times normal) and radiological investigation include USG abdomen and CT abdomen with findings suggestive of pancreatitis.

EXCLUSION CRITERIA:

Patients with more than 1 day abdominal pain even if the diagnosis is acute pancreatitis.

Patients with acute on chronic pancreatitis as revealed by previous history of pain or treatment.

Children < 14 years of age are not included in the study.

Patients with acute pancreatitis with gall stone disease , drug induced pancreatitis and other causes of pancreatitis.

Patients with disorders like rheumatoid arthritis, coronary artery disease, diabetes mellitus ,Obesity etc.., which increase serum CRP levels are excluded from the study.

Outcome measures:

Serial C reactive proteins levels were measured at 24, 48 and 72 hours were done after admission. Computed tomography with oral and IV contrast agents was done at 72 hours after admission and CT severity index (Balthazars and Ransons score) with CT grade and necrosis grade was ascertained.

All patients with severe pancreatitis (as per the Atlanta classification) were monitored and treated in surgical intensive care unit with continuous cardiac and respiratory monitoring and regular biochemical investigations including ABG while mild acute pancreatitis were treated in our surgical ward.

OBSERVATION AND RESULTS

Patients admitted to surgical ward with history and clinical examination suggestive of acute pancreatitis were selected.

After routine blood investigations,

Serum amylase and Serum lipase values were done followed by Ultrasonography of abdomen.

After confirmation of the diagnosis,only patients with history suggestive of alcoholic pancreatitis and who didnot have any other cause for pancreatitis are taken into the study.

Serial C reactive protein values were done at 24 hrs,48 hrs,72hrs from the time of admission by standard method and is compared with CT severity index which is assessed from contrast enhanced CT done at 3-5 days from the time of admission.

Necrosis score as given in the CTSI score is also compared and it’s correlation with serum CRP values ascertained.

Number of days of admission in the hospital is also recorded and is used as a marker of morbidity of the disease.

Significant Cutoff value for CRP was taken as 100mg/dl. Different studies cited in my study has given different values as significant (100 mg/dl and 150 mg/dl).In this study value of 100mg/dl was taken as significant because it was given in multiple studies and also correlated with our study results.

It has been already proved that peak levels of CRP are reached after 48 hrs of the onset of pain and so, in this study also the 48 hrs CRP values are compared with CTSI.

The current standard for assessment of severity and assessment of necrosis in patients with acute pancreatitis is CT severity index assessed by CECT with highest sensitivity and specificity and so is taken as the standard in this study to find the value of CRP in this regard.

CTSI value which correlates with severity of disease is given in multiple studies as more than or equal to 3,(i.e, presence of necrosis or if no necrosis present, collections in and around pancreas) which is also given as severe disease in Atlanta classification , is taken as significant to differentiate mild from severe cases.

Only one patient underwent necrosectomy in this study (indication-infected necrosis)and the patient survived the disease and was discharged on the 30th post operative day.

All patients with local complications and systemic disease are treated in intensive care setting and continuous monitoring done.

C reactive protein is a nonspecific marker and acute phase protein elevated in multiple inflammatory conditions and it is tried sincerely in this study to eliminate patients with already raised CRP by history and thorough clinical examination.

By assessing the correlation between CRP values and pancreatic necrosis, the value of CRP values to discern patients who need a CECT is ascertained.

Age distribution

Most of the patients included in the study are young to middle aged males and among them, pancreatitis is most common in the 30-40 year group(4rd decade of life).

Table 1.

Age group	21-30yrs	31-40yrs	41-50yrs
No of cases	8	27	15

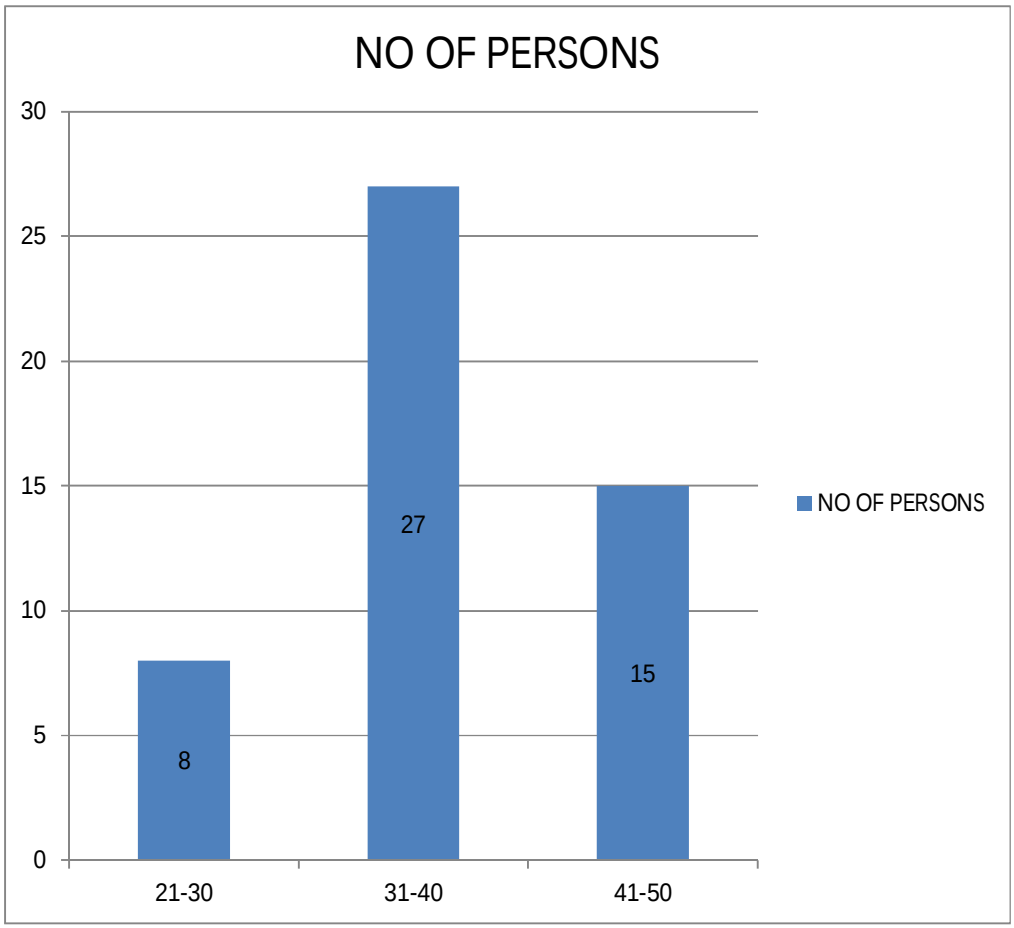


Chart.1 shows the age distribution among the patients in the study.

Etiological and gender distribution

Only male patients and alcohol induced pancreatitis patients are taken into the study and so etiological and genderwise distribution were not significant.

Serial CRP values distribution from time of admission.

CRP values continued to increase in patients with acute pancreatitis and peaks at 72 hours after admission.

Table 2

Time from admission(hours)	Average CRP values
24	**61.52**
48	**71.43**
72	**80.24**

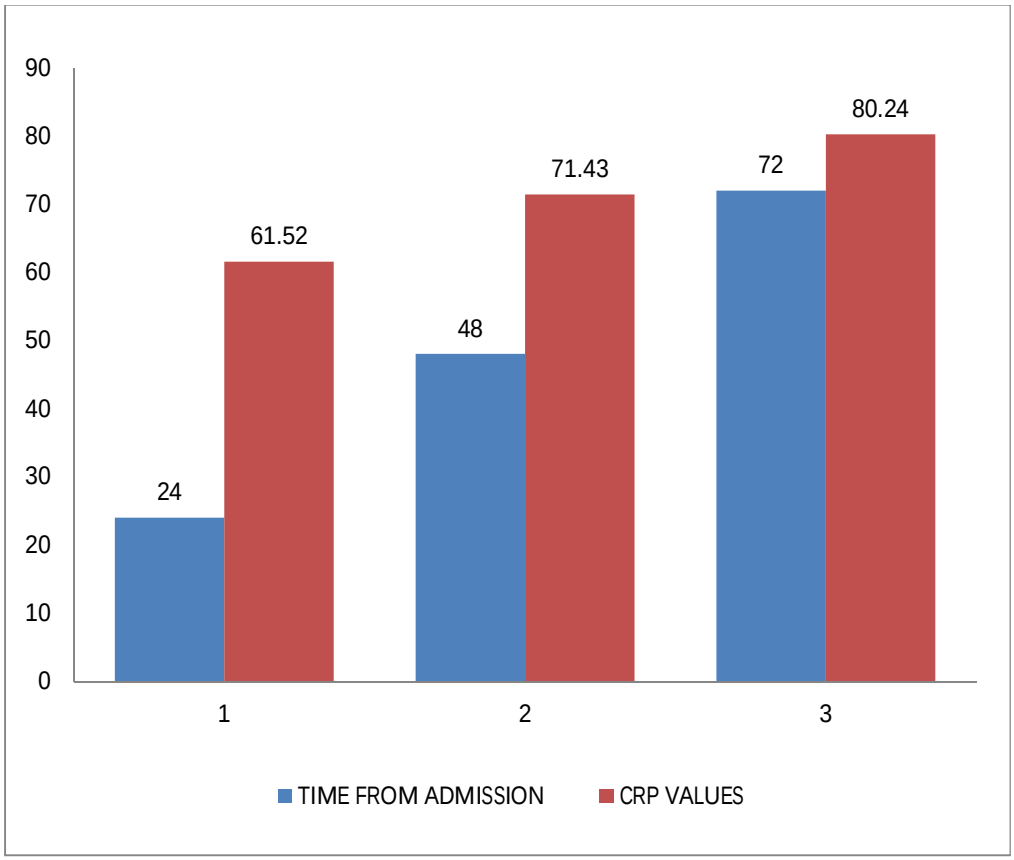


Chart.2 shows average CRP values serially from time of admission.

Average CRP values based on Age of patients

CRP values rise as the age of the group increases and highest values are seen in older age group.

Table 3.

Age group(yrs)	Average CRP values(48 hrs)
21-30	70.26
31-40	75.62
41-50	77.72

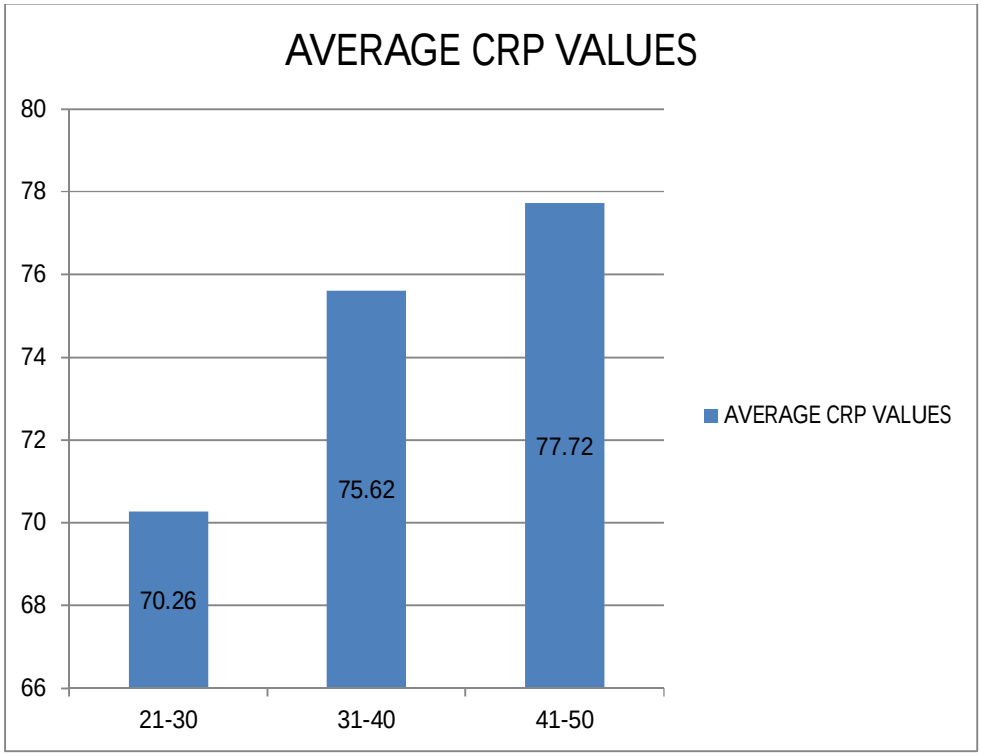


Chart.3 shows average CRP values(48 hrs) based on the age group.

Significant CRP values vs Duration of hospital stay.

Duration of hospital stay varied in different patients from 7days to 59 days(mean=26 days). Patients with CRP values >100mg/dl and values <100mg/dl are correlated with days of hospital stay in patients.

Table 4.

CRP values(mg/dl)	Duration of hospital stay(days)
<100 mg/dl	12
>100 mg/dl	25.2

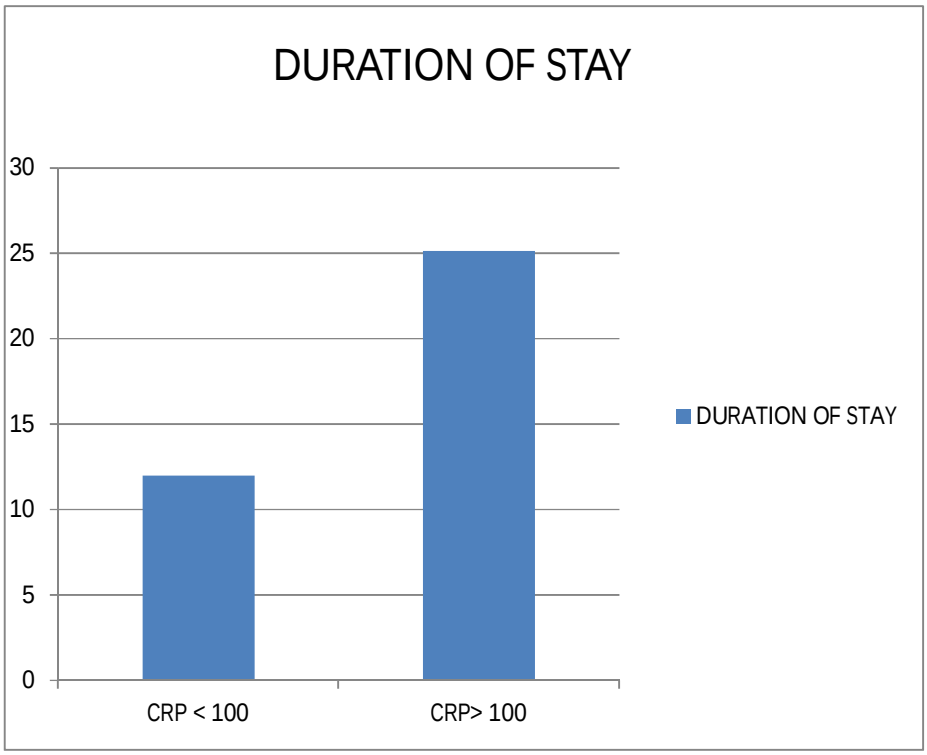


Chart.4 shows correlation of duration of hospital stay with significant CRP values.

Table 5 showing comparison of number of patients with significant CRP values at 48 hrs (>100 mg/dl) vs CT severity index values (>3).

	CRP value >100mg/dl (at 48 hrs)	**CRP values <100 mg/dl (at 48 hrs)**
CTSI >3 (total score)	11	2
CTSI <3(total score)	8	29

CALCULATION:

Sensitivity

number of true positives /true positives +false negatives

sensitivity = 84.61%

Specificity

Number of true negatives/true negatives+false positives

specificity =78.37%

Positive predictive value((PPV)

Number of true positives/true positive+false positive

PPV =57.9%

Negative predictive value

Number of true negative/true negatives+false negatives

NPV=92.54%

Table 6 showing comparison of number of patients with significant CRP value (48 hrs) with presence or absence of necrosis.

	CRP values>100mg/dl (48 hrs)	**CRP values<100mg/dl (48 hrs)**
Presence of necrosis (necrosis score+)	5	1
Absence of necrosis (necrosis score 0)	8	36

Sensitivity =83.33%

Specificity =81.81%

DISCUSSION

It is already known that CRP is a acute phase protein secreted by liver in multiple inflammatory conditions and is a non specific marker.

With this background,the major object of this study is to find the usefulness of Serum C reactive protein levels which is the most widely available and cheap inflammatory marker (Rafaele Pezilli et al,) in various aspects in setting of acute pancreatitis.

Of the 13 patients with severe acute pancreatitis as defined by Atlanta classification, all patients had CT severity index more than equal to 3 and so it is justified in using it as a standard to compare CRP values and it is the current standard in this regard as shown by number of studies.

As shown in other studies,peak values of CRP are reached at 48 hrs in our study and so values at 48 hrs are taken for the statistical analysis for comparison against CTSI.

As given in the literature,most of the therapeutic modalities employed in acute pancreatitis are useful only if instituted before 48 hours and eventhough CRP level is sensitive in giving the severity of disease,it cannot be considered as a very good indicator in this regard.

Significant value CRP level is given as different in multiple studies but, CRP level >100mg/dl as given in study by Meyer et al, correlates with values obtained in our study and so is taken as significant value for comparison.

Distribution of etiology and gender in pancreatitis could not be studied as most of the study group is constituted by young to middle aged males.

Average CRP values in subsequent decades of life is found to be increasing with average values being 70.26 in 3rd decade and 77.72 in 5th decade (chart 3) which also correlates with literature where it is stated that CRP values increase with age and elevated values are seen in old age.

Out of the 13 patients with severe disease,11 patients had CRP values more than 100 mg/dl giving CRP at 48 hrs a Sensitivity and Specificicity of 84.61% and 78.37% respectively,which correlates with earlier studies and establishes CRP level as a severity marker in acute pancreatitis with sensitivity and specificity better than the scoring systems (40-60%) as given by study by Gurleyik et al.(Table 5).

Out of 6 patients with necrotising pancreatitis with positive necrosis score in CTSI, 5 patients had CRP values at 48 hours

>100mg/dl giving CRP level sensitivity of 83.3% and specificity of 81.81% respectively (table 6)and by this data,it is established that CRP level can be used as an indicator for necrosis and to decide on patients with acute pancreatitis who need a CECT at 48-72 hours,since the investigation(CECT) is expensive and not widely available.

Average number of days of all patients in this study is 26,with the lowest being 7 days and the highest being 59 days. In patients with CRP level<100mg/dl , average duration of stay in hospital is 12 days and in patients with CRP values >100mg/dl, duration being 25.2 days (table 4) thus giving a positive correlation between CRP levels and the duration of stay in hospital and use of CRP level at 48 hrs as marker for the duration of stay in hospital and thereby as a indicator of morbidity is validated.

Some studies (Meyer et al) have done serial CRP values upto the 7 days and found that persistent elevation of Serum CRP values correlate with incidence of local complications(pseudocyst,abscess etc,)and the rate of need for surgery in the course of the disease,which couldnot be studied in this study as CRP values are measured only upto 72 hours from the onset of pain.

CONCLUSION

CRP as we know continues to be an acute phase reactant and a non specific marker of inflammation due to multiple etiology and it's values increase with increasing age of the patient.

Eventhough CRP level has good sensitivity and specificity in finding the patients with severe acute pancreatitis and it is better than most of the clinical scoring systems in sensitivity and specificity, it a poor marker in this regard as it's peak values are reached only after 48-72 hrs which is the therapeutic golden hour only within which treatments if instituted are rewarding as given in the literature.

But according to this study, it can be useful in the following regards.

Increased values of CRP above the significant range correlates positively with the occurrence of necrosis in pancreatitis and can be used to decide on patients who need a CECT as this investigation is expensive and is not widely available.

It correlates positively with duration of stay of patients in hospital thereby, giving the morbidity of acute pancreatitis.

Value of CRP levels in predicting the prognosis of the disease and the need for surgery for local complications remains to be elucidated.

LIMITATIONS OF THE STUDY:

1. Etiology could not be studied because the case group is ethanol induced pancreatitis is only selected for the study.
2. CRP being non specific marker of inflammation , exclusion of patients with already raised CRP is only by thorough history taking and questionnaire, but subclinical inflammatory conditions raising serum CRP levels could not be ruled out.
3. Clinical scoring systems were not included in this study.
4. Gender and age distribution could not be studied because the case group was all young and middle aged men and children < 14 years were excluded from the study.
5. Values were done only upto 72 hours and so the value of finding CRP in finding the need for surgery and thereby morbidity in patient by assessing CRP level at the end of 1 week could not be done.

BIBLIOGRAPHY

1. Gunay gurleyik ,Seyfi Emir,Gamze Kilicogh,Alper Arman, article titled computed tomography severity index APACHE II score and serum CRP concentrations for prediting the severity of acute pancreatitis. Jop. J pancreatitis (online 2005) , department of surgery, department of surgery and department of radiology hay darpara numme education and research hospital.Istanbul turkey.

2. AD meyer,MJ McMahon,Margaret Bowen,EH Cooper, article titled C reactive protein an aid to assessment and monitoring of acute pancreatitis j clinical pathol 1984 ,university , department Of surgery general infirmary leeds and the unit for cancer research , university of leeds .Leeds.

3. Raffacle pezzilli, Francesco Mansini, article titled assessment of severity of acute pancreatitis a comparison between old and recent modalities used to evaluate perennial problem. World journal of gastroenterology1999, august.

4. Chun Chia Chen, Article titled serum markers in the early assessment of acute pancreatitis which is most useful. J chin med assoc 2004:67:439-441Division of gastroenterology department of medicine . Taipei veterans general hospital and national Yang ming university school of medicine, Taiwan.

5. Ahmed z, article titled clinical laboratory assessment of acute pancreatitis. Clinica chimica acta (2005) 26-48, department of surgery Manchester royal infirmary. Manchester .

6. M.T Hamalainen , article titled do normal leucocyte and CRP on admission exclude a life threatening attack of acute pancreatitis. scandinarian journal of surgery 91-352-356, department of surgery university of turkey, finland.

7. Clinical pancreatology for practising gastroenterologists and surgeons / edited by J. Enrique Domínguez-Muñoz ; with foreword by Peter Malfertheiner. PANCREATITIS AND ITS COMPLICATIONS Edited by CHRIS E. FORSMARK, MD University of Florida College of Medicine, Gainesville, FL

8. Diseases of the Pancreas Current Surgical Therapy Edited by Hans G. Beger, Ulm, Germany Seiki Matsuno, Sendai, Japan, John L. Cameron, Baltimor*e*, USA.

9. Marja-Leena Kylänpää-Bäck, ACUTE PANCREATITIS: DIAGNOSIS AND ASSESSMENT OF SEVERITY WITH MARKERS OF INFLAMMATION**,**Department of Surgery and Clinical Chemistry, Helsinki University Central Hospital, and Department of Bacteriology and Immunology, Haartman Institute,Helsinki, Finland

10. Balthazar EJ, Freeny PC, Van Sonnenberg E. Imaging and intervention in acute pancreatitis. Radiology 1994; 193:297-306.

11. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. Radiology 1990; 174:331-336.

12. CANINE C-REACTIVE PROTEIN - a study on the applicability of canine serum C-reactive Protein, Mads Kjelgaard-Hansen, Ph.D.,Veterinary Clinical Pathology, Department of Small Animal Clinical Sciences. The Royal Veterinary and Agricultural University ,Frederiksberg, Denmark 2004.

13. M. Lempinen, P. Puolakkainen, E. Kemppainen, CLINICAL VALUE OF SEVERITY MARKERS IN ACUTE PANCREATITIS Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland, Scandinavian Journal of Surgery 94: 118–123, 2005.

14. Mitchell S. Cappell, Acute Pancreatitis: Etiology, Clinical Presentation, Diagnosis, and Therapy Division of Gastroenterology, Department of Medicine, William Beaumont Hospital, Royal oak, Clin N Am 92 (2008) 889–923.

15. Ranson JHC. Diagnostic standards for acute pancreatitis. World J Surg 1997; 21: 136–142.

16. Beger HG, Rau B, Mayer J, Pralle U. Natural course of acute pancreatitis. World J Surg 1997; 21: 130–135.

17. Buchler M, Malfertheiner P, Schoetensack C, Beger HG (1986) Sensitivity of antiproteases, complement factors and C-reactive protein in detecting pancreatic necrosis.Results of a prospective clinical study. Int J Pancreatol 1:227–235

18. Parimal Chowdhury, Priya Gupta, Pathophysiology of alcoholic pancreatitis: An overview, World J Gastroenterol 2006 December 14; 12(46): 7421-7427

19. Gullermo Robles-Diaz,Fred S.Gorelick, alcohol and Acute pancreatitis, Department of Medicine, Connecticut healthcare, West Haven, Connecticut, Yale journal of Biology and Medicine, 1997, pp.77-87.

20. Shakelford's Surgery of Alimentary Tract,5th edition ,edited by Mark B.Orrhinger and Richard Heitmiller.

Role of C-reactive protein as a severity marker in acute pancreatitis

Investigator: **Dr. S.Vignesh**, PGY2 – MS (Gen Surg)

Guide: **Prof. Dr. Balamurugan,** Chief, Unit S7.

Patient Information Module

You are being invited to be a subject in this study.

Before you participate in this study, I am giving you the following details about this trial, which includes the aims, methodology, intervention, possible side effects, if any and outcomes:

All patients diagnosed with acute pancreatitis by history,clinical examination and S.amylase measurement will be included in this study. A detailed clinical history will be taken following a standardized proforma. A detailed clinical examination will be made and relevant investigations, including basic and special investigations will be done.CECT abdomen and pelvis will be done at the time and 72hrs after admission and CTSI(CT severity index) according to BALTHAZAR grading will be found.All patients will be examined thoroughly and APACHE 2(acute physiology and chronic health evaluation score) will be ascertained.Serum CRP measurement will be done at the time and then after 24 hrs,48hrs&72hrs of admission.CRP values will be correlated with CTSI and APACHE 2 scoring.

The results arising from this study will be analyzed and used for academic purposes. You will be given clear instructions at every step and you are free to ask/ clarify any doubts. Your identity will remain confidential. You are free to withdraw from this trial at any point of time, without any prior notice &/ or without any medical or legal implications.

I request you to volunteer for this study.

Thanking You,

Investigator's Sign Patient's Sign

(Dr. S.Vignesh.) (Name:)

Role of C-reactive protein as a severity marker in acute pancreatitis

Investigator: **Dr. S.Vignesh**, PGY2 – MS (Gen Surg)

Guide: **Prof. Dr. Balamurugan,** Chief, Unit S7.

Informed Consent

Name: Age/ Sex: IP:

I herewith declare that I have been explained in a language fully understood by me regarding the purpose of this study, methodology, proposed intervention, plausible side effects, if any and sequelae.

I have been given an opportunity to discuss my doubts and I have received the appropriate explanation.

I understand that my participation in this study is completely voluntary and that I am free to withdraw from this study at anytime without any prior notice &/ or without having my medical or legal rights affected.

I permit the author and the research team full access to all my records at any point, even if I have withdrawn from the study. However my identity will not be revealed to any third party or publication.

I herewith permit the author and the research team to use the results and conclusions arising from this study for any academic purpose, including but not limited to dissertation/ thesis or publication or presentation in any level.

Therefore, in my full conscience, I give consent to be included in the study and to undergo any investigation or any intervention therein.

Patient's Sign **Investigator's Sign**
(Dr.S.Vignesh.)

PROFORMA

Role of C-reactive protein as a severity marker in acute pancreatitis

Investigator: **Dr. S.Vignesh**, PGY2 – MS (Gen Surg)

Guide: **Prof. Dr.Balamurugan,** Chief, Unit S7.

Name: Age/ Sex: I.P. No.:

Address: Contact no:

D.O.A: D.O.S: D.O.D:

History and Physical:

Vital parameters:

Pulse rate	
Blood pressure	
Respiratory rate	
Temperature	

Investigations:

HEMAT		
HB		
PCV		
RBC		
TC		
DC		
PLT		
ESR		
RBS FBS PPBS		
B.UREA		
S.CREAT		
S.Na+		
S.K+		
S.CI-		
S.HCO3-		

S.AMYLASE S.LIPASE	
USG	
CECT FINDINGS	
CT SEVERITY INDEX(BALTHAZAR SCORING) AND NECROSIS SCORE	time of admission: 72 hrs:

CRP LEVELS:

Time of admission	
24 hrs	
48 hrs	
72 hrs	

TREATMENT GIVEN:

TOTAL DURATION OF HOSPITAL STAY:

DISCHARGE NOTES:

FOLLOW UP:

S. No	Name	Age	Sex	I.P.No	CRP (24hrs)	CRP (48hrs)	CRP (72hrs)	Balthazar's score(CTSI)			no ofdays admission
								CT grade	necr-osis	total	
1	Dharmaraj	48	male	6362	32.6	40.8	66.5	1	0	1	8
2	Ashok	32	male	6764	106.2	110.2	110.8	3	0	3	27
3	Kumar	48	male	6931	31.7	34.3	40.2	1	0	1	6
4	Nelson	25	male	9795	83.9	101.1	120.4	2	0	2	15
5	Kowshar	32	male	11537	27	31.6	33.2	1	0	1	7
6	Arumugam	40	male	15993	110.2	118	135.8	3	4	7	38
7	Sampath	45	male	15997	123.4	137.6	162	4	6	10	59
8	Balakrishnan	45	male	16388	47.2	76.2	79.2	2	0	2	13
9	Gopi	30	male	18282	46.2	101.3	105.7	1	0	1	8
10	Baskar	48	male	19607	98.5	102.2	110.9	2	0	2	17
11	Kumar	35	male	20559	130.9	146.8	159	3	0	3	41
12	Amarnath	45	male	21144	21.3	28.3	34.9	1	0	1	6
13	Gopinath	24	male	21677	56.2	61.9	68.8	1	0	1	9
14	Purushothaman	34	male	22444	78.1	92.1	93.2	2	0	2	17
15	Nagaraj	34	male	26628	110.2	122.5	127.3	2	0	2	18
16	Muthukumar	43	male	26635	30.6	39.6	42.7	1	0	1	10
17	Sekar	32	male	31784	57.3	59	79.5	2	0	2	14
18	Loganathan	30	male	36450	36.9	52.3	78.4	1	0	1	7
19	Mohan	38	male	36395	98.5	99.2	106.8	3	0	3	16
20	Mani	37	male	38254	29.7	48.8	56.7	2	0	2	11
21	Tamilselvan	28	male	37322	80.2	106.3	120.2	2	0	2	13
22	Sivaji	36	male	39206	85.6	90	90	3	2	5	28
23	Ramesh	32	male	39214	18.2	24.5	30.9	1	0	1	12
24	Vishnu	37	male	22536	111	123	127	2	2	4	24
25	Deva	31	male	27904	11.3	17.2	19	1	0	1	10
26	Chandran	50	male	30091	120.1	136.2	139.7	3	2	5	35
27	Gopi	34	male	30558	42.9	48.5	56.6	1	0	1	8
28	Rajan	49	male	32774	38.9	42.8	57.6	1	0	1	7
29	Arunprasad	35	male	33278	31	39.7	48.5	1	0	1	10
30	Anandhan	42	male	35095	87.6	100.4	110.4	1	0	1	13
31	Muruganandham	43	male	37491	67.8	79.2	88.5	2	0	2	14
32	Vidyakumar	36	male	37469	15.3	31.7	33.2	1	0	1	13
33	Ramalingam	37	male	50086	102.3	104.3	118.9	3	2	5	33
34	Sekar	39	male	51069	53.7	59.8	72.6	2	0	2	19

35	Subramani	48	male	45243	52.2	57.8	67	1	0	1	15
36	Premkumar	29	male	46040	23.6	28.9	35.7	2	0	2	18
37	Prabu	31	male	955	92.4	101.2	109.7	1	0	1	16
38	Dhinakaran	36	male	2520	32	35.6	37.8	1	0	1	7
39	Ragavan	28	male	5252	21.9	28.3	34.4	1	0	1	11
40	Kathirvel	40	male	25020	97.2	110	121.5	3	0	3	17
41	Basha	37	male	28928	37.5	48.6	59	1	0	1	10
42	Rajan	35	male	33267	60.2	103.2	110.9	2	0	2	20
43	Kuppaiah	48	male	34231	34.9	38.6	43.2	2	0	2	15
44	Elumalai	30	male	39499	102	110	118.1	3	0	3	15
45	Mani	47	male	39529	15.7	17.8	17.9	1	0	1	13
46	Jothi	33	male	40787	35.6	45.8	47	1	0	1	9
47	Raghu	37	male	41382	41.7	59.5	67.1	2	0	2	17
48	Babu	33	male	42339	126.5	130.2	146.4	2	4	6	30
49	Veeran	43	male	42361	30.2	35.9	39	1	0	1	11
50	Suresh	40	male	48925	50.1	69.2	78.6	2	0	2	16